Goran Augustin

Acute Abdomen During Pregnancy

Second Edition

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WORLD SOCIETY OF
EMERGENCY SURGERY

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ISBN 978-3-319-72994-7 ISBN 978-3-319-72995-4 (eBook)
https://doi.org/10.1007/978-3-319-72995-4

Library of Congress Control Number: 2018940500

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To my father, an abdominal surgeon, whose ability to make an accurate diagnosis in emergency abdominal surgery only with history taking and physical examination was never outperformed. He taught me great things in this "clinical magic"
To my wife Katarina, who despite having two small children, understood the importance of this work to me and sacrificed almost a decade of many weekends, evenings, nights, and journeys to allow me and provide me enough time to create both the first and the second edition of this book
To my children (Lara and Lukas)... who remind me every day that teaching others is a great opportunity and pleasure that cannot be substituted
To my mother, whose mathematically functioning brain is fascinating, and now I realize that it is a fortune that I inherited most parts of it
And… to all pregnant women… who are healthy… and to all who need the clinicians' consultations from this book, whose lives and lives of their future babies will be saved and normal….

Foreword I

Diagnosis and treatment of surgical abdominal emergencies during pregnancy is challenging. Abdominal examination is difficult and organs may be pushed by the uterus in relation to gestational age, therefore obscuring abdominal pathologies. Physiological parameters are altered due to pregnancy-induced changes and laboratory tests could be deranged due to pregnancy-induced variations. In evaluating abdominal emergencies in the gravid women, the physician is advised to cautiously use tomography for diagnosis. Radiation exposure may affect the normal development of the fetus. Indeed a perplexing clinical setup.

Delay in the diagnosis of surgical emergencies is associated with amplified risk to the mother and the fetus. The need for nonobstetrical surgery during pregnancy is low. However nonobstetric surgery is fraught with increased risk to the fetus. Fortunately, in most cases, the gravid woman is a young and healthy individual and surgical emergencies are, therefore, confined to the young group of patients. The gestational risk in pregnant women with an acute abdomen is multifactorial. Some relate to the patient itself and her well-being and some relate to the fetal age of gestation at the time of diagnosis. Peritonitis and sepsis contribute to the risks, and surgical approach (laparoscopic vs. open) has a great deal of impact.

Dr. Goran Augustin has assembled data on surgical emergencies in the pregnant women and wisely outlined recommendations for the practicing surgeon faced with a gravid patient endangered with an abdominal surgical emergency.

Any surgery during pregnancy confers significant obstetrical risk. Delayed investigation and diagnosis may lead to worse outcomes for the patient and her fetus. Surgeons should be aware of pregnancy physiology and the precise algorithm for diagnosis and management during gestation. This book offers exactly that.

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Foreword II

I have been invested with the honor (and responsibility) of writing a "FORE" "WORD" meaning to write thoughtful comments made about a book, to give the impression as to what this book is all about. Acute abdomen during pregnancy is a dramatic event, with significant morbidity and mortality for both mother and fetus. Despite this, acute abdomen during pregnancy does remain a neglected and not well-known topic.

Clearly, a pregnant patient presenting with an acute abdomen is a clinical scenario that overlaps specialties. Common sense suggests the early involvement of a bunch of specialists such as a surgeon, obstetrician/gynecologist, and a specialist in maternal-fetal medicine when dealing with this challenging situation.

Unfortunately, the diagnosis and treatment often tend to be delayed due to the peculiar physiological features of pregnancy and the restrictions imposed on diagnostic imaging techniques such as X-ray and CT, due to the fear of radiation exposure. MRI is gaining an increasingly relevant role in the diagnostic workup but is not always and everywhere available or easily and readily accessible. Nevertheless, acute abdomen has the need to be diagnosed in the shortest time possible and promptly treated. Physicians should pay attention in this regard as any delay may seriously deteriorate the condition of both mother and fetus.

The editor, Dr. Goran Augustin, is an internationally recognized expert in the field of acute abdomen during pregnancy, and given his research and clinical activity from the last decade, I can wholeheartedly state that he is now considered an internationally recognized expert in the management of acute appendicitis and other acute surgical diseases in pregnant patients. His dedication to this critical subset of patients has to be commended, and Dr. Augustin has made this delicate issue to become his own area of clinical practice and his field of scientific research throughout the years. Textbooks and surgical journals are appearing to be the written resource of the fundamentals and the research reporting archives of the knowledge and the craft of this surgical discipline. This textbook is one of those resources and represents a landmark textbook in the field of the care of the pregnant patient. Both the trainee and the practitioner of acute care surgery but also gynecology and obstetrics as well as emergency physicians and family doctors will find this textbook useful and a ready resource for current approaches to surgical emergencies.

This will soon be a standard text used by surgeons who practice Acute Care Surgery around the world and any physician dealing with a critical surgical care during pregnancy, and it has been a privilege to review it.

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Preface to the Second Edition

He who combines the knowledge of physiology and surgery, in addition to the artistic side of his subject, reaches the highest ideal in medicine.

Christian Albert Theodor Billroth

I am fortunate again to have the opportunity of changing my mind, of clarifying confusion and my confused thinking, and of correcting misstatements, as well as attempting to remain contemporary. I am doomed to the embarrassment of living with my previous inaccuracies. Still, it is better to recant than to be accused of having a pertinacious little mind.

Marvin Corman
(Preface to the sixth edition of *Colon and Rectal Surgery*)

If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties.

Sir Francis Bacon

When I started writing the first edition of this book, I read the foreword of one book, from an author whom I do not remember, where he wrote that he did not know that it was more difficult and more time consuming to write the second edition of the same book. At first, I was surprised because I thought that one can change several figures and add a little new text, and the new edition is completed. When I started to improve the first edition, I recalled the author's words and his statement. It is the whole truth! I was surprised when, several months after the first edition was published, I started to read again my book. I was surprised how many misinterpretations, errors, or scientific and clinical "gaps" were present. I was ashamed how incomplete and inconsistent the book I wrote was. At the same time, I started to read the new, sixth edition of Marvin Corman's book – *Colon and Rectal Surgery*. Before going to the specific topics that interested me, I read the preface. And I was thrilled, relaxed, satisfied, and fulfilled at the same time. The citation that I took from Corman's *preface* is true. Then, it was easier to finish this second edition knowing the fact that it will be better than the first edition (and probably worse than future editions). Every chapter is expanded and updated, and four new chapters are added. The chapter on urologic emergencies helps to differentiate conditions that usually do not require operative interventions. Perioperative and anesthetic considerations, which were the part of every chapter in the first edition, are concentrated in a separate chapter and significantly expanded. Many of these considerations are the same for most acute abdominal conditions during pregnancy. One of the added chapters is especially interesting. It is about increased intra-abdominal pressure during

pregnancy. This issue is complex even in the general population, and in pregnancy, it has additional difficulty during the diagnostic workup and also with the selection of appropriate treatment strategy for both the mother and the fetus.

My father, who was also an abdominal surgeon, watched me while writing the second edition, for 2 years, day by day. Once, he came to me, knowing that I am the sole editor and author, and said: “This book is concentrated energy, so much energy that could fill an atomic bomb.” Now, when the text is finished, I can confirm that his statement is true. Concentrated energy or concentrated knowledge is what I want to share with every reader!

And now, I repeat my plea from the preface of the first edition: contact me about any type of errors, misinterpretations, and any medical/surgical mistakes in the text because I would like to improve (further editions of) this interesting subject. Dear authors, publish cases of the acute abdomen during pregnancy, and publish comprehensive reviews, so the medical community could have a better insight into the incidence, etiology, diagnosis, treatment, and maternal and fetal outcome for all causes of the acute abdomen during pregnancy. Dear reviewers and editors of medical journals, please have a sensibility for these important topics. Who knows, maybe, one day, a journal, for example, *Journal of Abdominal Surgery in Pregnancy* or *Digestive Diseases in Pregnancy*, will be created.

Zagreb, Croatia Goran Augustin

Preface to the First Edition

The art and science of asking questions is the source of all knowledge.

Thomas Berger

What has given me the most joy in my life is the establishment of a school that carries on my aspirations and aims, be it scientific or humanitarian thereby ensuring a legacy for the future.

Theodor Billroth, 1893

Earlier diagnosis means better prognosis.

Zachary Cope, 1921

How did the idea for the book come? Here is the answer. Acute abdomen is still one of the most exciting conditions in (emergency) surgery and medicine in general. The clinician needs to make the diagnosis and the indication for the operation as fast as possible, and then the operator should perform the operation with the lowest possible morbidity and mortality. This is known for over a century. An additional difficulty arises when that clinician has a pregnant patient with acute abdomen. Now he or she is dealing with two human beings at the same time. Also, the pregnant patient has slightly changed intraperitoneal anatomy and physiology, making the diagnosis more difficult.

During the last 7 years, I started to study more about cases of the acute abdomen during pregnancy. Searching through the literature, I found very little reviews on the subject. Unfortunately, that was expected because acute abdomen during pregnancy is a rare group of conditions. If one excludes the most common causes such as acute appendicitis and acute cholecystitis, the clinician can deal with only one pregnant patient having acute abdomen in several years, sometimes once in a career. When I comprehended that, I started to study, write, and publish articles about different topics of the acute abdomen during pregnancy. When I tried to find some texts covering the whole topic, I could not find these. Then, it came to me that I need to write a book about *acute abdomen during pregnancy,* first to help myself and then to help all the clinicians dealing with this rare subject. It is interesting that some names in medicine, gynecology, and surgery who are not so famous or known were the first to treat such cases in medical history. It was interesting for me to read about them and to put them in the book. Mostly, these persons were more famous for other achievements in their medical fields.

There are two problems in writing a book that should have guidelines and recommendations on the topics included. First, it is the (extreme) rarity of these diseases. Second, it is the acute onset that is unpredictable in its severity

and time of presentation. Both these facts preclude the possibility for randomized studies that are needed for validated guidelines and recommendations in medicine. Therefore, some of the recommendations in the book are not adequately validated, but due to the rarity (some diseases have less than 50–100 cases published in 100 years), I tried to combine the recommendations from acute abdomen in the general population and from the opinions of the authors (and myself) of published case reports. Thus, many facts from these case reports are copied into this textbook. Also, the comprehensiveness of the chapters is not equal and mostly depends on the frequency of a specific condition during pregnancy. Hence, the most extensive chapters include acute appendicitis and acute cholecystitis, the conditions which present most of the cases of the acute abdomen during pregnancy. I tried to include as much as possible case reports, so the reader can have his or her own opinion about the topic and also can develop ideas for further research on the subject. After completing the manuscript, I read it thoroughly, and then I realized that there are many things that could be written better. What motivated me to go further is Margaret Atwood's tip for writers: "If I waited for perfection, I would never write a word." Therefore, if I waited for perfection, I would never write this book.

Additionally, it should be mentioned that possibly any cause of acute abdomen can occur during pregnancy and a detailed description would lead to an enormous number of unnecessary pages; therefore, in conditions that have only one or several cases published, a short description of the disease is presented. It is difficult to say if this book is more suitable for the gynecologist or general/abdominal surgeon. Some parts will be more interesting to the surgeon, while others more to the gynecologist, especially therapeutic considerations. The diagnostic workup will be interesting to every reader. Some photos (figures) in the text are not of the excellent quality, but because of the extreme rarity of some conditions, it is impossible to obtain other figures of similar or same pathology.

And my final plea… to every reader… please contact me about any type of errors, misinterpretations, and any medical/surgical mistake in the text because it would improve (further editions of) this interesting subject. Contact me if you have any questions about the subject. Also, any reader dealing with this subject could feel free to contact me to be an author of one of the chapters in (possible) further editions of this book. My other plea to the reader is to publish cases of the acute abdomen during pregnancy so the medical community could have a better insight into the incidence, etiology, diagnosis, treatment, and maternal and fetal outcome for all causes of the acute abdomen during pregnancy.

I hope that the reader will enjoy reading the book as much as I enjoyed creating it!

Zagreb, Croatia Goran Augustin

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Part I

Surgery

1 Acute Appendicitis

Abstract

Acute appendicitis is the most common non-obstetric operative emergency during pregnancy. It amounts to 25% of operative indications for the acute abdomen during pregnancy and puerperium. Pain in the right lower quadrant is the most reliable symptom, and abdominal tenderness is almost always present. Fever and tachycardia are not sensitive signs. Leukocytosis is not diagnostic because elevated levels are found during pregnancy and especially in the early labor in normal pregnancy. Neutrophil granulocytosis is diagnostic as it is a sign of bacterial infection. Graded abdominal ultrasound is the diagnostic procedure of choice with less accuracy in the third trimester with no guidelines about the use of transvaginal ultrasound. Magnetic resonance imaging is the diagnostic procedure of choice in cases when abdominal ultrasound is not diagnostic. Management is always surgical, either by open approach or laparoscopy. Fetal mortality in uncomplicated appendicitis is low and rises several times when perforation and diffuse peritonitis develop. Maternal mortality is almost 0% and rises with the delay in surgery for more than 24 h which is the most common situation in the third trimester when the diagnosis is the most difficult.

1.1 Historical Perspective

It proves fatal to a woman in a state of pregnancy, if she be seized with any of the acute diseases.
Hippocrates

A case described by Stumpf in 1836 (reference unavailable), as one of ruptures of the cecum in a pregnant woman, was probably an early instance of perforative appendicitis. Officially, the first case was in 1848, when Henry Hancock (Fig. 1.1), the President of the Medical Society of London, presented a paper to that society describing the treatment of a 30-year-old female, in her fifth pregnancy, 7 months pregnant bearing twins in the Charing Cross Hospital in London [1]. She developed abdominal pain, had preterm labor on the fourth day with a live newborn for 20 h, and developed a tender mass in the lower right abdomen. She was seen by Hancock, 12 days after the disease has started. She had distended, tender abdomen, particularly in the lower right quadrant (RLQ). Hancock prescribed opium and poultices. Two days later her condition was much worse with a palpable mass in the RLQ. The incision was made above and parallel to Poupart's ligament over the palpable mass. When the abdomen was opened, offensive pus and bubbles of gas escaped. After 2 weeks she

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_1

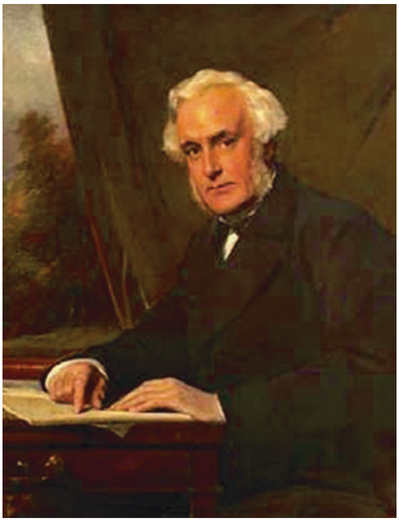

Fig. 1.1 Henry Hancock (1809–1880) (oil on canvas, 91 × 71 cm, painted by *George Richmond* in 1874; collection: The Royal College of Surgeons of England). Reproduced with permission

felt pain around the wound, and after wound exploration, Hancock found two fecaliths which he postulated that had escaped by ulceration from the diseased appendix. From that time her improvement was rapid and she made a good recovery. Therefore, Hancock is the author of the first reported and successfully operated AA complicating pregnancy in a form of incision of perityphlitic abscess but with stillbirth as a consequence.

Wiggins, in 1892, reported the first case in which the preoperative diagnosis was made and an operation advised at a time when the life of both mother and infant could have been saved. Unfortunately, the patient's friends refused the operation. Petersen, in 1893, recorded the first postpartum case of AA on the seventh day following a labor at term, with rupture of the abscess into the bowel and recovery without operation [2]. In 1894, Paul Fortunatus Mundé (1846–1902), a gynecologist from Mount Sinai Hospital in New York, published the first successful case from the United States [3], treating appendiceal abscess but with the premature delivery of a dead child.

1.2 Incidence

Appendicitis or epityphlitis (*epi*- + Greek *typhlon* (cecum) + -itis, inflammation) is the most common nonobstetric cause of acute abdomen during pregnancy and puerperium. Between 1913 and 1926, approximately 2–2.5% of the women who presented with symptoms of AA were pregnant [4, 5]. In 1935 the incidence of AA during pregnancy was 1/2000 [6], while between 1944 and 1959, the incidence was 1/1000 [7, 8], and a report from 1972 claimed an incidence of 1/704 [9]. It was concluded that AA is a disease of modern civilization, caused by a sedentary life and a high-residue flesh diet [10]. Current estimates of incidence are inconsistent and vary widely ranging 1/181–1/8770 pregnancies and amount to 25–30% of operative indications for the acute abdomen in pregnancy [11–30]. The rate of AA reported during the antepartum in the most recent four population-based studies is 1/1000–1/4167 pregnancies [20, 25, 31, 32]. The highest incidence is in Taiwan—1/181 [11]—and varies significantly between countries and even between regions and hospitals in the same country (Table 1.1). Although there are no references that specifically address postpartum AA, most studies group AA in pregnancy and the puerperium together because of the anatomic and physiological continuum [33]. Up to 1960, there were 373 cases published [34], and currently, the largest population-based study was on over 7100 appendectomies during pregnancy [32]. Analysis across trimesters is presented in Sect. 1.3.2.

Table 1.1 Comparative incidence of acute appendicitis in pregnancy in different countries

Country	Incidence
Taiwan [11]	1:181
Pakistan [23, 35]	1:346–1:1135
Germany [22]	1:499
Sweden [27]	1:776
Chile [36]	1:1028
Israel [37]	1:1055
Saudi Arabia [26]	1:1102
Turkey [13]	1:1312
Jordan [29]	1:1644
Brazil [30]	1:2580
Mexico [28]	1:8770

1.3 Risk Factors

1.3.1 Age and Multiple Pregnancies

A high incidence of AA in pregnancy, compared to other causes of the acute abdomen during pregnancy, has a multifactorial origin (Table 1.2). The incidence of AA and childbearing is strongly related to age. Ninety percent of pregnant women are <30 years of age [38], correlating with the peak incidence of AA in the general population [39]. The incidence of AA shows regional variations and a secular trend with a decreasing incidence in general population. Secular and regional variations are also seen for the incidence of childbirth. The influence of these variations on the incidences of AA and pregnancy is complex which makes it difficult to determine the expected incidence of AA during pregnancy for comparison purposes. Early marriage and repeated pregnancies till menopause make the probability of an AA occurring in pregnancy higher.

Table 1.2 Risk factors for acute appendicitis during pregnancy

Age <30 years
Multiple pregnancies
Second trimester (perforated and negative)
Black and Hispanic women
Nonobese
Attacks of appendicitis before pregnancy
Pregnancy-induced constipation
Medicaid insurance

1.3.2 Trimester

It seems that AA is more common in the second trimester with the incidence of 35–50% [22–24] (the first 30%, the second 45%, the third 25% [20, 38, 40, 41]), but there are no proven data that pregnancy affects the overall incidence [42]. Figure 1.2 illustrates a comparison of pregnancy status at the time of surgery in women who had an appendectomy compared with matched controls [43]. Patients who had undergone appendectomy were less likely to be pregnant at the time of the operation compared with controls. This inverse relation was dependent on the period of gestation and the underlying diagnosis at the operation. Corroborating results from previous reports, the highest incidence of AA and appendectomy was found in the second trimester of

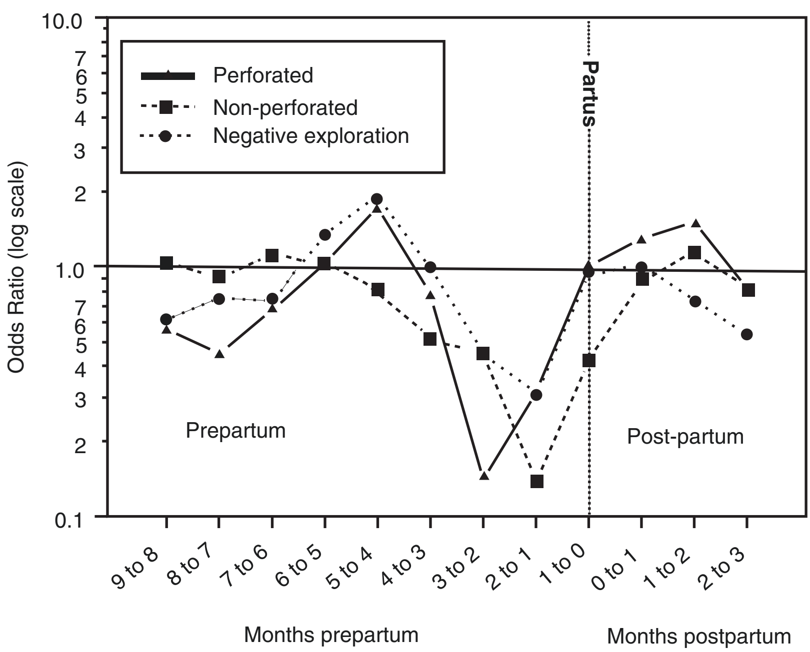

Fig. 1.2 Comparison of pregnancy status at the time of surgery in women who had an appendectomy compared with matched controls. The relation is expressed as the odds ratios according to conditional logistic regression. Reproduced with permission from [43]

pregnancy. This pattern was seen for perforated AA and negative explorations, whereas for nonperforated AA, the strength of the inverse relation increased continuously throughout the pregnancy. This result does not support the commonly expressed opinion that the incidence is the same in pregnant as in nonpregnant women but rather suggests that pregnancy may protect against AA (Fig. 1.2).

In the largest study to date, a national representative cohort of almost 1.6 million childbearing women, pregnant women during the antepartum period were 35% less likely to be diagnosed with AA than the time outside pregnancy (Fig. 1.3), with the lowest risk reported during the third trimester.

These results were not materially changed after adjusting for age and calendar year. Furthermore, there was no increased risk of AA in the postpartum period compared with the time outside pregnancy among women aged 15–34 years. However, the risk increased by almost twofold in older women during the later postpartum [31]. It is possible that AA during pregnancy, at term, and in the puerperium is lower or underestimated due to several reasons. The first is unrecognized mild, self-limiting disease [44–46]. Mild attacks could be interpreted as the ordinary discomforts of pregnancy, and the severe cases occurring in the puerperium were probably regarded as types of puerperal sepsis. Also, these attacks could be interpreted as intestinal colic, renal colic, ureteropyelitis, threatened miscarriage, salpingitis, and tubal pregnancy. The second is that one should be cautious with the term AA during labor. Sometimes labor is induced by inflammatory changes due to AA (see Chap. 23) [45]. The third is that some claim that there is a reduced incidence especially in the third trimester because of the protective (immunomodulatory) effect of pregnancy (see Sect. 1.4.1) [43], the fact stated back in 1921. The conclusion was that "In the last few weeks of gestation and during labor it is very rare" [47]. It was found at term in 1% of the pregnant population [48].

1.3.3 Other

The largest, population-based study showed the significantly higher proportion of Black and Hispanic women compared with the proportion of nonpregnant women with AA [32]. As early as 1905, it was found that patients with conservatively treated suspected acute or chronic appendicitis had significantly higher incidence of AA during pregnancy, some claiming more than 50% (see Sect. 1.4) [44, 49, 50]. Pregnant women with

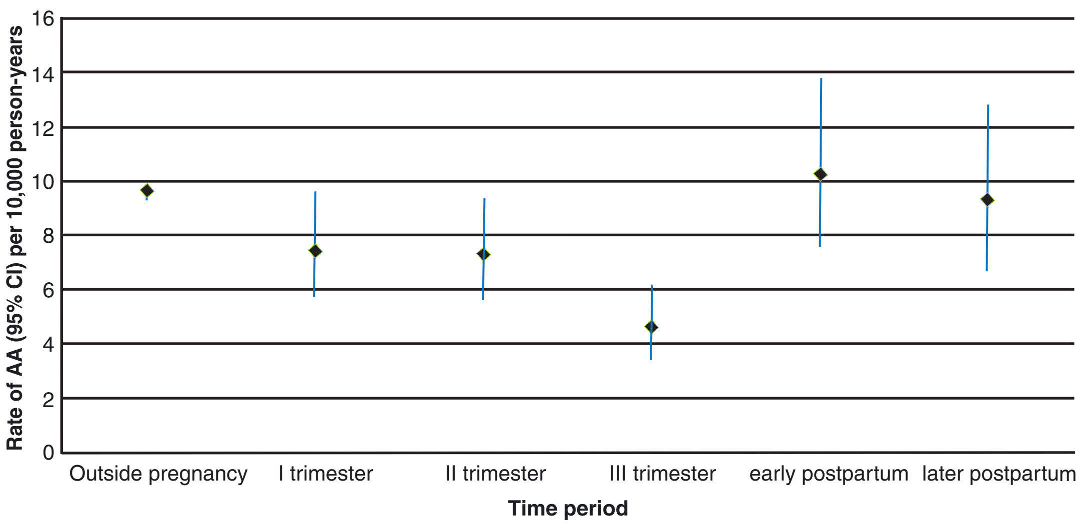

Fig. 1.3 Absolute rates of acute appendicitis per 10,000 person-years by trimesters and early and later postpartum period in England. Reproduced with permission from [31]

AA were less likely to be obese and more commonly had Medicaid type of insurance [32]. Constipation is given as an etiological factor in the nonpregnant women, and this risk factor is also accepted as one of the risk factors in the pregnant population [51].

1.4 Pathogenesis

It is still not possible to presume when AA would develop because etiology and pathogenesis are not completely known and understood. One of the confirmed etiologies of AA is mechanical obstruction of the appendiceal lumen, either due to fecal stasis, kinking, peritoneal adhesions, or infection-induced swelling of the mural lymphoid tissue. Other mechanisms include a breakdown of the mucosal barrier in the appendix by the direct invasion of a pathogen or by an inflammatory response that has been triggered by an infectious agent or some other stimulus. Geographical differences in the incidence in AA and secular trends in general population have been related to the differences and changes in the dietary intake of fiber and in standards of hygiene [52, 53].

1.4.1 Immunologic Changes

During pregnancy, a range of physiological changes take place that may influence the pathogenesis of AA. The immune system is shifted toward a T-helper cell type 2 (Th_2)-dominated immunity with a depressed cellular inflammatory response and increased humoral immunity [54]. A decrease in T-helper cell type 1 (Th_1)-mediated chronic inflammation is particularly present in the third trimester [43, 55, 56]. These changes may cause an exacerbation of diseases, such as asthma and an improvement of other ones, such as inflammatory bowel diseases during pregnancy [57, 58]. There is an overall decrease in proinflammatory cytokine trajectories in the innate and adaptive arms of the immune system and an increase in counter-regulatory cytokines as pregnancy progresses [59]. Because AA is an inflammatory process, the inverse relationship between pregnancy and AA could suggest that a Th_1-mediated inflammatory response is partly responsible [58]. This mechanism influences only the inflammatory and not obstructive type of AA. Moreover, cigarette smoking has a proinflammatory effect [60] and is reported to be associated with an increased risk of AA in general population [61]. Because pregnancy may motivate women to quit smoking [62, 63], this could also partially contribute to the lower risk of AA observed during pregnancy. Inflammatory markers have a dose-dependent and temporal relationship to smoking and smoking cessation. Smoking-associated inflammatory response returns to normal within 5 years after smokers quit [64].

1.4.2 Anatomic/Physiological Changes

In general population, the incidence of AA is higher in men. It has been suggested that the vascular anastomoses which exist in women between the blood vessels of the appendix and the ovarian vessels on the right side may have an important bearing on this comparative immunity. These anastomosing channels would serve to relieve congestion and inflammation of the appendix by carrying off some of its blood into the systemic circulation [49]. This mechanism does not have any effect in the obstructive form of AA.

Progression of AA may be more fulminating in pregnancy for various reasons. Increased pelvic vascularity and displacement or kinking (especially if partly fixed) of the appendix by the uterus may hasten obstruction or strangulation, and increased local lymphatic drainage together with interference with omental migration due to enlarged uterus may favor the systemic spread of the inflammatory process. It is thought that *Braxton-Hicks contractions* prevent the formation of adhesions, thereby promoting early diffuse peritonitis [18, 34, 38, 65]. Also, suppuration takes place higher in the abdomen. The abdomen can handle suppuration much better in the lower than in the upper parts. When the inflammation and suppuration occur, abdominal viscera start to localize the process by encircling

it. In pregnancy intestines and greater omentum are dislocated. Also, abdominal viscera expect localization of the process cease movement, while the uterus does the reverse increasing the possibility of spreading suppuration and making the diffuse peritonitis more likely. With the ascent of the uterus, the adnexa and appendix are brought into closer proximity. Infection in either may cause a corresponding inflammation in the other by contiguity. Around 1900, the communication by lymphatics, by a *peritoneal fold of Clado*, the appendiculo-ovarian ligament was claimed. This is a fold of peritoneum which is prolonged outward from the infundibulopelvic ligament to the mesoappendix [66].

1.4.3 Recurrent/Chronic Appendicitis

Pregnancy does not seem to predispose to a primary attack of AA; but if a patient has previously suffered from the complaint and afterward becomes pregnant, the pregnancy may light up another attack. The explanation for recurrent attacks in pregnancy lies in the vascular engorgement of the appendix, in the constipation which is commonly associated with pregnancy, in the toxemias of pregnancy, in the encroachment of the uterus in the early months of pregnancy, and in the puerperium and, finally, in the occasional presence, by stretching or breaking down old inflammatory adhesions, binding the appendix to the uterus and its appendages. While these factors doubtlessly tend to incite a recurrent attack of AA, it cannot be said that these create a primary attack [44, 49–51].

1.4.4 Female Sex Hormones

A relation with female sex hormones has been proposed because of a lower incidence among women and incidence variations during the menstrual cycle, but with inconsistent results [67, 68]. Childbearing constitutes a period of many hormonal fluctuations, although the time scale for these hormonal and immunologic changes may be measured in weeks. The dynamic maternal immune responses to normal pregnancy have evolved out of the need to support a semi-allogenic fetus over the duration of the pregnancy, without significant infectious or inflammatory impediment to the mother.

1.5 Clinical Presentation

1.5.1 Medical History

The approach to pregnant patients with severe abdominal pain is similar to that for nonpregnant patients. However, the anatomical/physiological changes associated with pregnancy must be considered when interpreting findings from the history and physical examination. The uterus enlarges about 20 times during pregnancy resulting in stretching of supporting ligaments and muscles, as well as pressure on other intra-abdominal structures and layers of the anterior abdominal wall (Fig. 1.4). Immediately after delivery, the uterus assumes a 15–16 week size [69]. At 1 week postpartum, the uterine fundus returns to the pelvis and is the size of a 12 week gravid uterus. After the first week, uterine involution occurs more slowly, reaching prepregnancy size within 6 weeks (Fig. 1.5).

During the first 6 months of pregnancy, symptoms and signs of AA are same as in nonpregnant woman, but still, there are difficulties in the diagnosis due to:

- Blunting/masking of symptoms and signs (abdominal distention, intra-abdominal organ dislocation, diminished tissue response to inflammation)
- Possible changes in appendiceal location as pregnancy advances
- Nausea, vomiting, and abdominal pain of normal pregnancy especially in the first trimester
- Extensive differential diagnosis with the addition of pregnancy-related diseases

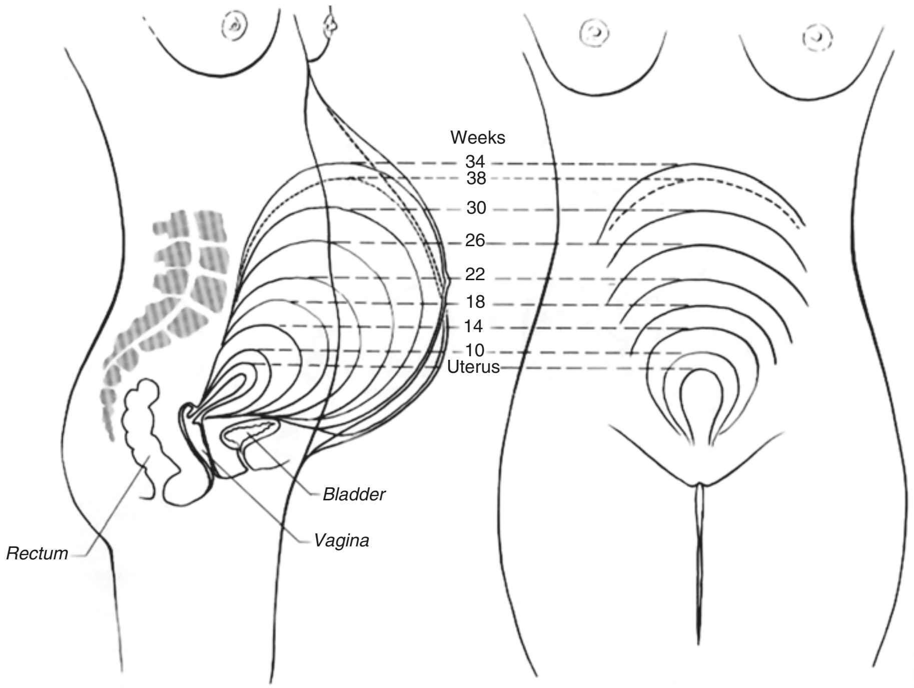

Fig. 1.4 Height of the fundus at comparable gestational dates varies greatly from patient to patient. Those shown are most common. Convenient *rule of thumb* is that at 5 months' gestation, fundus is usually at or slightly above the umbilicus. Reproduced with permission from [70]

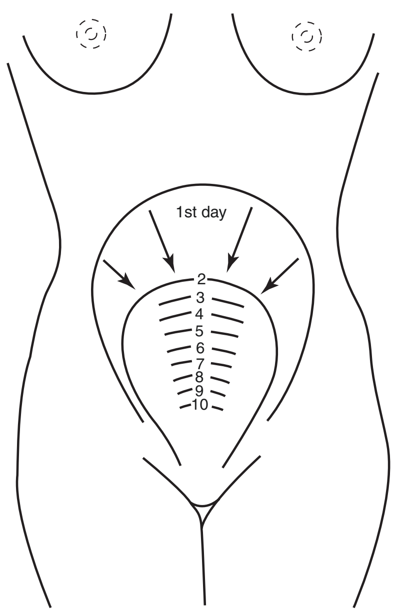

Fig. 1.5 Postnatal shrinking of the uterus. Reproduced with permission from [70]

- Working diagnosis of systemic infection
- Misleading obstetric complications that could be the first sign of nonobstetric intraperitoneal infection

Constant abdominal pain is the most common symptom [15], and pain in the RLQ, present in 67–84% of patients, is the most reliable symptom [15, 18, 19, 27, 38, 71]. The incidence of RLQ pain is trimester dependent with lowering incidence during trimesters (100%, 80%, and 60%, respectively) [72]. Rates of pain localized in the RUQ range 10–42% [38, 73, 74] and are most common during the third trimester [23]. Classical pain migration is highly suspicious of AA and is present in around 50–70% of patients [27, 75]. After the third month of pregnancy, the pain could change location and move progressively upward and laterally reaching the level of the right iliac crest at the end of the sixth month of pregnancy. Upward displacement of the cecum and appendix

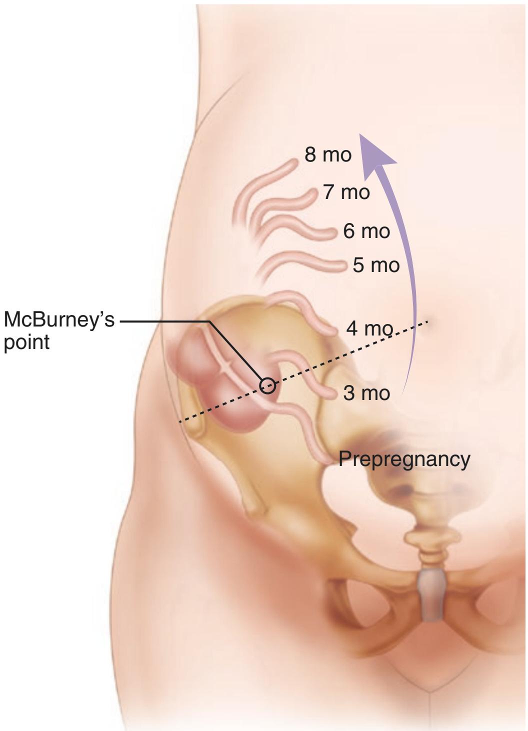

Fig. 1.6 Change of the location of the appendix during pregnancy; illustration by Chris Gralapp [86]

was first described by Füth in 1905 and 1913 [76, 77]. At that time Hoffman in 1920 stated that the appendix is below the iliac crest in 90% of pregnant women and that the exact position of the cecum during pregnancy can be defined only by abdominal X-rays with barium enema [78]. Baer et al. [79] showed by barium enema that the growing uterus progressively displaces the appendix out of the pelvis after the third month, into the upper right quadrant, by as much as two fingerbreadths above McBurney's point, with a counterclockwise rotation of the tip (Fig. 1.6). The appendix returns to its normal position by postpartum day 10. Original description by McBurney is that pressure is applied by one finger "exactly between 1½ and 2 in. from the anterior spinous process of the ileum on a straight line drawn from that process to the umbilicus." This landmark corresponds to the areas of the inflamed appendix irritating the abdominal peritoneum over the T_{11} and T_{12} dermatomes. The pain and hyperesthesia are present over McBurney's point in spite of the possible upward displacement of the appendix [80], and many have found no evidence of upper displacement of the appendix using physical examination, imaging techniques, or intraoperatively [24, 78, 81–85]. Positional changes may be hampered by the presence of adhesions which restrict the free movement of the appendix, especially the retrocecal (subserosal) position. Hodjati and Kazerooni found the significant change (>2 cm) in the position of the appendix in 15–23% of patients [84]. This discrepancy is partly due to different extent of cecal fixation.

> A growing pregnant uterus could displace a mobile cecum with the appendix but not the completely/partly fixed cecum or (retrocecal) appendix.

Recent publications using MRI confirmed the upward displacement of the appendix in the term pregnant woman [87, 88]. The most difficult interpretation of abdominal pain is immediately before, during, and immediately after the labor. Before labor when uterine contractions are present, one should be cautious if the patient has significant abdominal pain between contractions or if the pain is present after delivery [46].

Abdominal pain aggravated by fetal movements is found in a small percentage of cases [51, 89, 90].

Nausea is nearly always present and vomiting in 70–87% of patients [85]. These symptoms are exaggerated due to (1) progesterone-induced delayed gastric emptying and (2) pressure of enlarged uterus on the hollow viscus. The patient should be evaluated with caution because many women with normal pregnancies have these symptoms especially in early pregnancy [27]. Suspicion should be raised if new-onset nausea is present (the period of nausea and vomiting in early pregnancy is mostly self-limiting and confined to the first trimester).

Anorexia is present in one-third to two-thirds of pregnant patients, while it is present almost universally in nonpregnant patients [17, 18, 91]. If new-onset anorexia is present, it should raise suspicion, especially if present with other symptoms and signs suggesting AA.

An atypical clinical picture is most commonly present in the second trimester [22]. RUQ pain

(12%), uterine contractions, dysuria (20%), and diarrhea could mask AA [24, 26, 42, 71].

In cases of pregnancy when obstetric complications such as *miscarriage* [49] or *preterm labor* [92–94] occur, if the symptoms have previously pointed to any abdominal or pelvic symptomatology or a complication, a careful examination should always exclude AA which could cause these obstetric complications. These obstetric presentations as possible consequences of AA in pregnancy were pointed out back in the nineteenth century [95–97].

1.5.2 Physical Examination

The abdominal wall also undergoes significant change during pregnancy, with muscle tone reduction and skin elasticity to accommodate the enlarging uterus. The abdominal wall tone remains lax for several weeks postpartum, returning to a near-nonparous level in 6–7 weeks. The hallmarks of the acute surgical disease, abdominal guarding and rigidity, do not occur or are attenuated during the early puerperium. The chronic stretching of the parietal peritoneum by the growing uterus, in particular in the third trimester, decreases the number of afferent sensory nerve fibers of the peritoneum per square. There is a high circulatory level of adrenocorticoids in pregnancy which tends to diminish the tissue response to inflammation and to mask the early signs of infection and hinder localization. Increased separation of parietal and visceral peritoneum by an enlarging uterus causes decreased perception and localization of somatic pain. All these changes make clinical localization of inflamed appendix unreliable.

There is not a single, completely reliable sign that can aid in the diagnosis of AA in pregnancy, and some of the classic signs of AA such as Rovsing's and psoas signs have not been shown to be of clinical significance in diagnosing an AA in pregnancy [26].

An *abdominal mass* may be missed on physical examination because of the presence of the enlarged gravid uterus [98].

> *Abdominal tenderness* in the RLQ on direct palpation is always present [71, 85, 99].

Rebound tenderness is present in 55–93% [23, 71, 85, 91, 100, 101] and *abdominal muscle rigidity* in 50–65% [23, 40]. These two signs are more likely to be present during the first trimester. In the second and the third trimester, as the abdominal wall distends, the anterior abdominal wall is distanced from the inflamed appendix losing the ability to elicit guarding and rigidity [42, 102].

Rovsing's sign is present in 50–60% of patients [19, 23, 101], and trimester distribution is not known. Possibly it is rarely positive in the third trimester due to the separation of the abdominal wall from the colon, without the possibility of its compression.

The psoas sign (*Obraztsova's sign*) is a pain on passive extension of the right thigh when the inflamed appendix is in a retrocecal/retroperitoneal location in contact with the psoas muscle. The psoas muscle is stretched by this maneuver. The psoas sign is observed less frequently during pregnancy (5–50% [101, 103]) when compared with nonpregnant patients with AA [17].

Obturator sign is positive in 21% of patients [101].

Rectal or pelvic tenderness may occur in early pregnancy but is unusual in late pregnancy as the appendix is dislodged from its pelvic location and shielded with the enlarged uterus [102, 104]; therefore, less than half of patients had tenderness on rectal examination [100, 101].

Alder's sign is used to differentiate between AA and tubo-ovarian pathology in RLQ pain in pregnancy and puerperium [105]. The practitioner should find the point of maximal tenderness while the patient is supine. Then roll the patient onto the left side. If pain shifts toward the center, then it may be tubo-ovarian. The problem in pregnant patients in the third trimester is that the enlarged uterus does not allow the tubo-ovarian complex to shift its position. It is obvious that this sign can be of use only if the uterus is not large enough to be palpable abdominally and that it may be misleading in the rare case in which a uterine lesion has become fixed by adhesions to the anterior abdominal wall. In acute salpingitis, which does occur in pregnancy, the result of the test will depend on the presence or absence of perisalpingitic adhesions. In one study 36% of patients with proven AA had positive Alder's sign [101], without comparison between trimesters.

Aaron's sign is a referred pain or discomfort felt in the precordial or epigastric region when continuous firm pressure is applied over McBurney's point [106].

Bryan's sign is abdominal pain produced by shifting the gravid uterus to the right, by some the most reliable sign [107].

The *mean maximal axillar temperature* is 37.2–37.9 °C but could be over 39 °C in cases of perforation and diffuse peritonitis [15, 34, 85]. Unfortunately, only up to 50% of pregnant patients with AA have a low-grade fever [23, 85, 108]. In one series 72% of patients who had AA (with or without perforation) had temperatures of less than 37.5 °C [100]. This incidence of elevated temperature is not different from the normal pregnant population, and the finding is also true for *tachycardia* [41, 108], and both are not sensitive signs [24, 109], predicting only perforation and peritonitis. Also if normal pregnant patients have a low-grade fever, they have leukocytosis, a fact that further complicates definitive diagnosis [85].

1.6 Differential Diagnosis

Differential diagnosis is more extensive than in nonpregnant patients because of:

- Less reliable history and physical examination
- Higher incidence of some pathologic conditions that mimic AA

These conditions are presented as nonobstetric/non-gynecologic and gynecologic/obstetric conditions (Table 1.3).

Table 1.3 Differential diagnosis of acute appendicitis during pregnancy and puerperium

Nonobstetric/non-gynecologic conditions	Gynecologic/obstetric conditions
Gastroenteritis	Ruptured/hemorrhagic ovarian cyst
Urinary tract infections	Adnexal torsion
Pyelonephritis	Salpingitis
Nephrolithiasis	Tubo-ovarian abscess
Acute cholecystitis	Threatened abortion
Acute pancreatitis	Placental abruption
(Incarcerated) hernia	Chorioamnionitis
Bowel obstruction	Pelvic inflammatory disease
Cecal carcinoma	Degenerative fibroid
Mesenteric adenitis	Ectopic pregnancy
Spontaneous rectus hematoma	Preeclampsia
Pulmonary embolism	Round ligament syndrome/pain
Right lower lobe pneumonia	Varicose veins in the parametria
Meckel's diverticulitis	Preterm labor
Sickle cell disease	Pelvic endometriosis
Stump appendicitis	Metritis
Inflammatory bowel disease	Ovarian vein syndrome

1.6.1 Round Ligament Pain/ Syndrome

Round ligament pain or syndrome (RLP) is one of the most common discomforts of pregnancy and, usually, starts at the second trimester of gestation and continues until delivery. It usually resolves completely after delivery, although cases of several days postpartum RLP have been reported. The most common symptoms of RLP are a sudden pain in the lower abdomen, usually on the right side of the pelvic area that can extend to the groin, and shooting abdominal pain when performing sudden movements or physical exercise. Pain is sudden and intermittent and lasts only for a few seconds. Although very common during pregnancy, non-gestating women can also experience RLP. The most common causes of RLP are:

1. Round ligament spasm or cramp when the ligament contracts involuntarily. The ligament pulls on nerve fibers and sensitive structures of the female reproductive system. Since the uterus tends to be oriented toward the right side, the pain is also often felt on the right side. This leads to frequent confusion with AA [110].
2. The increase in size and weight of the uterus puts stress on the ligament that holds it, causing it to stretch. During physical exertion or sudden movements, the ligament is overly stretched, causing pain.

3. Varicosities [111], e.g., enlargement of the blood vessels of the round ligament, can occur during pregnancy, causing pain and swelling. The varicocele starts at the veins draining the round ligament and the inguinal canal and is associated with engorgement of the veins of the ovaries and the pelvis during pregnancy.
4. Endometriosis [112, 113] that infiltrates or borders the uterine round ligament can cause RLP in fertile, non-gestating women.
5. Other pathologies that involve the uterine round ligament can cause RLP.

However, diagnosis of RLP is problematic. Some of the conditions that may present symptoms similar to those of RLP are AA, ectopic pregnancy, kidney stones, urinary tract infection, uterine contractions, inguinal hernia, ovarian cysts, and endometriosis. If abdominal pain is continuous and accompanied by vaginal bleeding, excessive vaginal discharge, fever, chills, or vomiting, then it is most unlikely to be RLP, and immediate specialist consultation is warranted [113]. Physical examination, ultrasonography, and blood and urine tests may define the cause of abdominal pain. In some cases, however, RLP was diagnosed only during exploratory surgery [111, 114, 115].

1.6.2 Stump Appendicitis

Stump appendicitis is an acute inflammation of the residual part of the appendix and a rare complication of an incomplete appendectomy. It can present clinically as AA and/or as an appendiceal stump/perityphlitic abscess. It was first reported by Baumgartner in 1949 [116], and currently, 60 cases are published and found after open as well as after laparoscopic appendectomy (LA) in general population [117]. There is only one case report in pregnancy where fimbriae of the right Fallopian tube were stuck on the appendiceal stump end-to-end. The chorioamnionitis resulted with preterm delivery [118].

1.6.3 Meckel's Diverticulitis

Symptomatic Meckel's diverticulum/diverticulitis (MD) during pregnancy is exceptionally rare. Wenzl in 1949 published the first case of MD in a pregnancy [119]. Only 27 cases of MD-complicated pregnancy have been reported from 1949 to 2016 [120–125]. The average maternal age in symptomatic MD was 24 years (14–31 years). The most common presentation was MD perforation (57%) [123]. In the non-pregnant adult population, on the other hand, perforation of MD occurs in 7.3–26.8% [126–128]. In general population, bleeding is the most common presentation in patients younger than 20 years [129, 130] and is rare beyond the age of 30.

Preoperative diagnosis in pregnancy is difficult (up to 2002 in only 9% [123]) because even on transabdominal ultrasound, it can mimic AA, as noncompressible tubular structure (see Sect. 1.7.5).

1.6.4 Crohn's Disease

See Chap. 8.

1.6.5 Urolithiasis/Urinary Tract Infection

The difference in the sequence of events in AA and pyelitis is important in differentiating them. In AA the findings are first pain, later fever, and rarely chills. In pyelitis chills come first and then fever and pain. See Chap. 20.

1.6.6 Vomiting of Pregnancy

Even in 1905, Heaton explained the difference between AA and vomiting in pregnancy. "The illness may be of all degrees of severity, from the transient appendiceal colic to the fulminating AA which proves fatal in a few hours. In the mild cases, the sickness which ushers in the illness is liable to be mistaken by both patient and

practitioner for the ordinary vomiting of pregnancy. The use of the clinical thermometer in a doubtful case should prevent mistake, for the vomiting of pregnancy is 'apyrexial,' and the presence of fever, however slight, should always put us on our guard and lead us to make a careful examination of the right iliac region" [49]. Unfortunately, low-grade fever is present in only 50% of patients with AA (see Sect. 1.5.2).

1.6.7 Fitz-Hugh-Curtis Syndrome

Perihepatitis (Fitz-Hugh-Curtis syndrome) is the result of early bacteremic or retroperitoneal lymphatic dissemination of *C. trachomatis* or gonococcal pelvic infection [131]. The syndrome is most frequently seen in young women and is more common in the second and third trimesters and puerperium. Inflammation in the RUQ produces perihepatic adhesions. Classically, there is sudden onset of sharp RUQ pain, often pleuritic in quality. Nausea and hiccups are occasionally noted. Physical findings include tenderness under the right costal margin, an occasional hepatic friction rub, and fever. Pelvic examination may be normal or may reveal signs of cervicitis or pelvic inflammatory disease. Liver function tests and cholecystogram may be transiently abnormal. The diagnosis is suggested by a history of recent pelvic infection, but the syndrome can be a sequel of latent or asymptomatic infection. The diagnosis is further supported by isolation of gonococcus on cervical culture and improvement on appropriate antibiotics [131]. It is important to exclude other etiologies because there is no specific diagnostic marker of this syndrome.

1.6.8 Puerperium-Associated Diseases

1.6.8.1 Metritis

The most common of these is *metritis,* the broad group of postpartum infections of the genital tract. Metritis is often insidious in onset. Because of the vague initial manifestations, it is often a diagnosis of exclusion. Endometritis, or deciduitis, is an infection of the most superficial layer of the uterus and is the most common site of puerperal infection. The onset of endometritis is commonly 2–5 days postpartum, and the earliest manifestations are malaise, anorexia, and fever. There may be no localizing signs or symptoms in mild cases. The pelvic examination may be normal, even in the presence of severe endometritis. The disease may progress further to involve the myometrium (myometritis) and parametrial structures (parametritis) with extension into the broad ligaments, tubes, ovaries, and pelvic peritoneum [69]. When the parametria are involved, pain and tenderness are present deep in the groin. Extensive infection may produce lethargy, chills, high fever, and significant lower abdominal pain, tenderness, and rebound. An accompanying paralytic ileus may cause distention and vomiting. Myometritis and parametritis are usually accompanied by localized peritoneal signs and cervical motion tenderness but rarely generalized peritonitis. The lochia may provide a clue as to the true nature of the difficulty. Within 48 h the lochia of an endometritis becomes serous, seropurulent, or foul smelling if the infection is saprophytic. A flare-up of a gonorrheal salpingitis seldom begins before the seventh day, and the findings usually are limited to the pelvis. A positive history of the previous infection is important for the diagnosis.

1.6.8.2 Pelvic Thrombophlebitis/Ovarian Vein Syndrome

Thrombophlebitis and thromboembolic events occur significantly more often in pregnancy especially puerperium. Ovarian vein thrombosis complicates less than 0.05% vaginal deliveries and 1–2% of Cesarean sections (CS) [132]. Ovarian vein thrombosis involves the right ovarian vein in 90% of cases, which has been attributed to retrograde flow in the left ovarian vein and antegrade flow in the right ovarian vein in the postpartum period. This difference in blood flow may be attributable to the physiologic dextrorotation of the uterus during pregnancy and compression of the right ovarian vein. Women in the puerperium are predisposed to deep vein thrombosis attributable to sluggish circulation, trauma to the pelvic vessels during delivery,

immobilization, and estrogen-mediated hypercoagulability.

Other risk factors include abortions, gynecological surgery, malignancy, pelvic inflammatory disease, Crohn's disease, and infections with *Campylobacter fetus* and group A streptococcal bacteremia. Underlying inherited thrombophilia primarily factor V Leiden mutations and protein S deficiency has been reported in 50% of patients with ovarian vein thrombosis. There are cases of ovarian vein thrombosis associated with antiphospholipid syndrome and heparin-induced thrombocytopenia type II.

Pelvic thrombophlebitis, or right ovarian vein syndrome, commonly presents with abdominal/pelvic pain (66%), fever (80%), and a tender midabdominal or RLQ mass [132]. However, the diagnosis is often complicated by the other nonspecific symptoms and signs: back pain, nausea, vomiting, tachypnea, tachycardia, hypotension, ileus, and sepsis [133]. It may be difficult to distinguish from metritis but should be strongly considered if there is a poor response to appropriate antibiotics or exclusion of adnexal torsion (see Sect. 12.6). Diagnosis can be delayed due to fever and elevated laboratory inflammatory parameters that often mislead to the diagnosis of AA, urinary tract infection or tubo-ovarian abscess [134].

The diagnosis is frequently made after a fever is nonresponsive to antibiotics after 48 h. Color Doppler sonography is the first diagnostic procedure [135], but due to low sensitivity and high false-negative and false-positive rates, IV contrast CT scan is preferred. The sensitivity of IV contrast CT (Fig. 1.7) is 100%, while that of MRI with gadolinium contrast 92% and duplex color Doppler ultrasound 50% [136].

Untreated postpartum ovarian vein thrombosis carries the risk of serious complications like sepsis and extension into the inferior vena cava. Septic pulmonary embolism occurs in 11–33% with an overall mortality of 4–5% [138]. Anticoagulation for 3–6 months with low-molecular-weight heparin and a course of antibiotics for 2 weeks are the mainstay of treatment offering cure to a high proportion of patients. The surgical treatment is reserved for patients in

Fig. 1.7 Abdominal CT scan showing thrombosed right ovarian vein (*arrow*). Reproduced from [137] under the CC BY 2.0

whom anticoagulation is contraindicated and those who develop treatment-related complications and are at high risk for pulmonary embolism—those with free-floating thrombus, an extension of thrombus, or recurrent pulmonary embolism despite adequate medical therapy [139, 140]. Surgical interventions include ligation and splitting of the thrombosed ovarian vein and inferior vena cava or placement of inferior vena cava filters to prevent pulmonary embolism.

No uniform guidelines exist for evaluation of thrombophilia after ovarian vein thrombosis. Pregnancy and the puerperium are hypercoagulable states, which may predispose women to develop ovarian vein thrombosis. The risk factors associated with postpartum ovarian vein thrombosis reported positive results for several thrombophilias, including antiphospholipid syndrome, lupus anticoagulant, factor V Leiden mutation, MTFHR C677T deficiency, and protein S deficiency [141]. However, the *American College of Obstetricians and Gynecologists* recommends testing white women with a previous deep vein thrombosis for the factor V Leiden mutation and individualizing testing in nonwhite women [142].

1.7 Diagnosis

Medicine is a science of uncertainty and an art of probability.

William Osler

Until recently, negative appendectomy rates (NARs) of up to 50% in pregnant women have been tolerated, given the consequences of missing an AA and the understanding that no test or combination of tests existed with sensitivity and specificity above 80–85% [143]. Also, a pregnant woman's physiologic leukocytosis, increased heart rate, and respiratory alkalosis make her more likely to meet clinical criteria for systemic inflammatory response syndrome than a nonpregnant woman (plus a possibility of a delayed diagnosis of localized inflammatory disease) [144].

These are the reasons why all investigations must occur in the hospital. Diagnostic workup should be done on an interdisciplinary basis in cooperation with the obstetrician. There was no significant difference in the median time from presentation to first imaging test or surgery, the incidence of negative pathology, or the appendiceal rupture between women who presented to the ED compared with those who presented to obstetric triage [145]. The lag time between arrival to the emergency room and laparotomy was significantly higher in the second half of pregnancy compared to the first half, being 11.6 and 7.7 h, respectively [37]. Clinical and ultrasound examination is less reliable in the second half of pregnancy.

Physicians may be reluctant to order a radiological study because of the potential teratogenic risks to the fetus as well as the medicolegal implications of the radiation dose causing birth defects. For acute indications, the benefits for the mother usually outweigh the small risk to the fetus. The greatest effects of radiation occur during the period of rapid cell proliferation (2–25 weeks of pregnancy). The recommended total dose of radiation during this time is less than 5 rad. During the first 2–3 weeks of pregnancy, while cells are not yet specialized, radiation injury will cause failure of implantation or undetectable death of the embryo. After that, the injury usually occurs in the organs under development at the time of exposure.

> *No single diagnostic procedure results in a radiation dose that threatens the well-being of the developing embryo and fetus.*
> American College of Radiology [146]

> *The fetal risk is considered to be negligible at 5 rad or less when compared with the other risks of pregnancy, and the risk of malformations is significantly increased above control levels only at doses above 15 rad.*
> National Council on Radiation Protection [147]

Exposure to less than 5 rad (50 mGy) has not been associated with an increase in fetal anomalies or pregnancy loss [148]. Also, there are fetal risks during normal pregnancy: 3% risk of spontaneous birth defects, 15% risk of spontaneous abortion, 4% risk of prematurity and growth retardation, and 1% risk of mental retardation [149]. These data should be explained to the future mother.

1.7.1 Laboratory Findings

Leukocytosis (raised white blood cell count—WBC) is not diagnostic due to the physiologic rise in some pregnant patients in the second and third trimesters reaching 20,000/mm^3 in early labor [150]. For the orientation, the values over 16,000/mm^3 should raise serious suspicion [19, 24, 40, 109, 143]. Unfortunately, only 60% of those with perforation had values over 16,000/mm^3 [27]. If there is clinical suspicion of AA with normal values of WBC, serial WBC counts (every 6 h) may be helpful [151, 152], or comparison with previous WBC measurements during normal pregnancy could help. If WBC values during previous normal pregnancy were within normal limits, then RLQ pain with elevated WBC should be taken seriously.

Neutrophil granulocytosis with left shift: the presence of increased proportions of younger, less well-differentiated neutrophils and neutrophil precursor cells in the blood is diagnostic of acute infection. If left shift is not present, then granulocytosis of more than 80% should raise suspicion of AA [85]. In some studies bands were not elevated on the WBC differential, making a high band count not specific in these patients [24, 153].

A *raised C-reactive protein* (CRP) could be a normal finding during pregnancy and especially delivery and possibly protects the mother from the injury and mechanical effects of labor. After delivery in normal pregnancy, values increase 10- to 20-fold (never >10 mg/L) when compared with those recorded at admission, and these increased levels may be associated with host defense mechanisms [154]. Pregnant patients with gestational diabetes, diabetes mellitus, obesity, or pregnancy-induced hypertension have elevated CRP levels but up to 10 mg/L [155–158]. Despite racial differences, CRP levels are also never over 10 mg/L [159]. CRP increases bacterial phagocytosis and promotes the clearance of dead cells. Therefore, CRP is of little assistance in establishing the diagnosis [27], but with other clinical symptoms and signs of AA, it confirms the diagnosis when elevated over 10 mg/L. Some studies claim that all positive cases had negative CRP values if the patients were evaluated less than 12 h after the onset of pain [109]. Sixty-eight percent with AA had CRP ± 10 mg/L, but all patients with perforation had elevated CRP (mean 55 mg/L) [27].

The *erythrocyte sedimentation rate* is physiologically elevated and thus is a less reliable monitor of inflammatory activity during pregnancy [160].

Leukocyturia (57%) and bacteriuria (41%) are common findings in patients with AA [71]. This may also represent concurrent asymptomatic (or symptomatic) bacteriuria found frequently in pregnant population [17]. Other abnormalities such as *mild proteinuria* and/or *hematuria* could be present in up to 19% of pregnant patients [100].

Puerperal changes in blood components may be confusing as well. During the first 10–14 days of the puerperium, WBC counts of 20,000–25,000/mm^3 are not unusual; there is also a predominant increase in neutrophils. The erythrocyte sedimentation rate may increase to 50–60 mm/h. Reliance on either the erythrocyte sedimentation rate or the WBC count for the diagnosis of acute infection may be misleading [69].

1.7.2 Diagnostic Scoring Systems

Isolated clinical signs and blood indices are unreliable for the diagnosis of AA in pregnancy and lead to an unacceptable NAR, up to 50% when imaging studies are not used [37]. Therefore, several clinical-imaging scoring systems have been developed for a more precise diagnosis of AA in nonpregnant population but without larger studies in the pregnant population.

1.7.2.1 Alvarado Score and Modifications

The most commonly used score in nonpregnant population is the *Alvarado score* described in 1986 [161] and has been extensively validated. The mnemonic is MANTRELS (Table 1.4). Currently, there is no specific scoring system for pregnant patients, and *Alvarado score* [162] and *modified Alvarado score for pregnant patients* [163] have been used in small series of patients. When Alvarado score 7

Table 1.4 Comparison of Alvarado score and modified Alvarado score for pregnant patients

Alvarado score		Modified Alvarado score for pregnant patients	
Symptoms	Score	Symptoms	Score
Migratory RLQ pain	**1**	RLQ pain	**2**
Anorexia	1	Anorexia	1
Nausea/vomiting	1	Nausea/vomiting	1
Signs		Signs	
Tenderness in RLQ	2	Tenderness in RLQ	2
Rebound tenderness in RLQ	1	Rebound tenderness in RLQ	1
Elevated temperature (≥37.3 °C/≥99.1 °F)	1	Elevated temperature (≥37.3 °C/≥99.1 °F)	1
Laboratory		Laboratory	
Leukocytosis (>10,000/mm^3)	2	Leukocytosis (>10,000/mm^3)	1
Shift to the left (>75%)	1		
Total score	**10**	**Total score**	**9**

was used as a cutoff, the NAR was 15% [162]. The difference in comparison to the standard *Alvarado score* is that migration of pain is not included and the number of points just for the pain in RLQ is 2 in comparison of 1 point in the standard *Alvarado score* for the nonpregnant population. Leukocyte left shift is not included, and leukocytosis (which could be present in a normal pregnancy) has only 1 point in *modified Alvarado score for pregnant patients*, and the total score is lower for 1 point (9 vs. 10) (Table 1.4). Positive predictive value was 60% in Alvarado score range of 5–7 and 100% in a score range of 7–9. In the same study, the sensitivity of ultrasound was 78.6%.

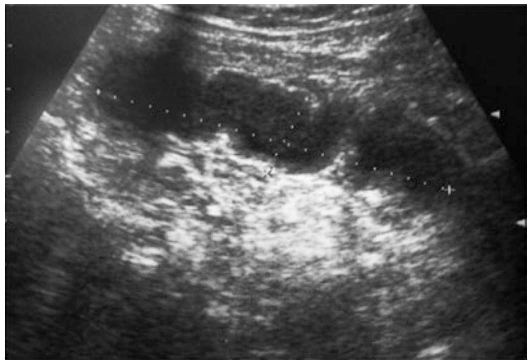

Fig. 1.8 Ultrasonography of the abdomen shows a tubular cystic structure measuring 8 cm × 2 cm in the right iliac fossa, found to be giant Meckel's diverticulitis. Reproduced with permission from [125]

1.7.3 Transabdominal Ultrasound

As a noninvasive procedure, it is considered by the *American College of Radiology Appropriateness Criteria* the initial imaging modality of choice for suspected AA in pregnancy [164]. Sonographic criteria are the same as in the nonpregnant population for the diagnosis of AA [165]:

- Noncompressible appendix
- Appendiceal diameter >6 mm
- Appendiceal wall thickness ≥2 mm
- Free fluid around appendix
- Complex mass in the area of the appendix

Indirect signs include abnormal fluid collections in the pelvic cavity or around the cecum/appendix. Evaluation of the entire length of the appendix may be difficult in a pregnant patient with an enlarged gravid uterus, and it is not surprising that the focal area of AA may be missed by using standard techniques. In many instances, AA is morphologically evident only on its tip, which is sometimes not visualized [165].

The reported sensitivity and specificity vary dramatically. The reported sensitivity ranges from 66% to 100% [71, 160, 165–171] to only 40–50% [85, 172]. In few large studies, it was nondiagnostic in up to 70–88% of patients [20, 173]. Because its positive predictive value is almost 100%, it provides confirmation of the diagnosis when it is positive. Sometimes differentiation between (giant) MD and AA on ultrasonography can be difficult because both are noncompressible tubular structures in RLQ (Fig. 1.8).

However, the diagnosis of AA could not be ruled out if negative. The use of this technique with the patient supine is difficult during the late second trimester and third trimester of pregnancy because the large size of the gravid uterus does not allow graded compression. For women in the late second trimester or third trimester, it is recommended that the patient is placed in the left posterior oblique or left lateral decubitus position, which allows displacement of an enlarged uterus and use of the graded-compression technique without difficulty [166]. There is a significant reduction in the NAR in the ultrasound/CT scan group compared to the clinical evaluation group or the ultrasound group. Thus, an ultrasound followed by a CT scan in patients with a normal or inconclusive ultrasound is recommended [171]. Currently, almost 100% of patients are submitted to abdominal ultrasound preoperatively [15, 171].

1.7.4 Transvaginal Ultrasound

There are no *Royal College of Obstetricians and Gynaecologists* guidelines about the use of transvaginal ultrasound. The US Food and Drug Administration (FDA) has proposed an upper

limit of 720 mW/cm^2 for the spatial-peak temporal average intensity of the ultrasound beam for an obstetric ultrasound [174].

Transvaginal ultrasound can be used to look for the following features [175]:

- Presence and size of adnexal or uterine pathology which can rule out AA
- Free fluid in the pouch of Douglas
- Pathology in the ileocecal region (cecal tumors, cecal diverticula, or retroperitoneal tumors)
- Acute appendicitis (aperistaltic, tubular structure measuring ≥6 mm, hyperemia, appendicolith, free fluid around the appendix) (Figs. 1.9 and 1.10)

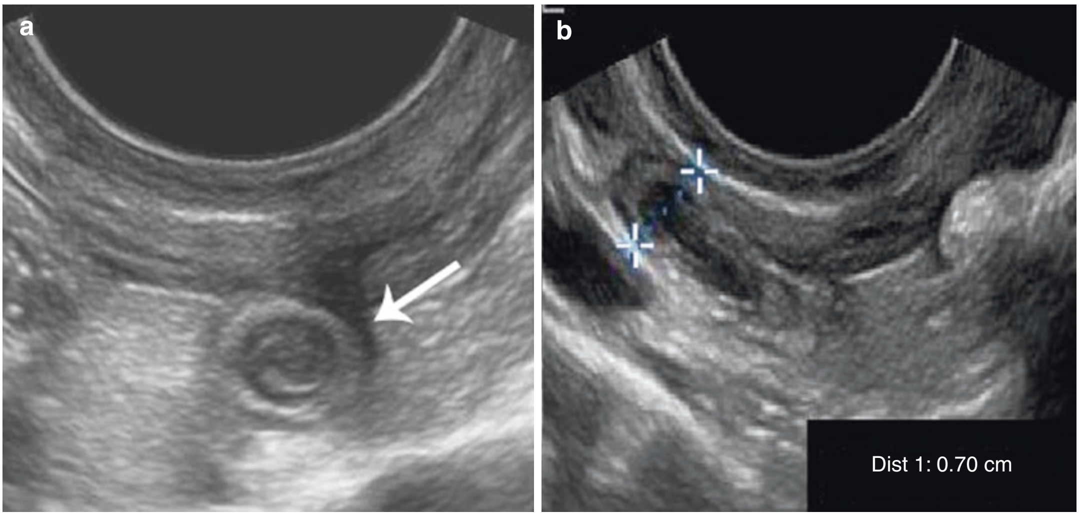

Fig. 1.9 Transvaginal imaging of the right adnexa. (**a**) Transverse view of the appendix. (**b**) Long view of the appendix measuring 0.7 cm. Reproduced with permission from [176]

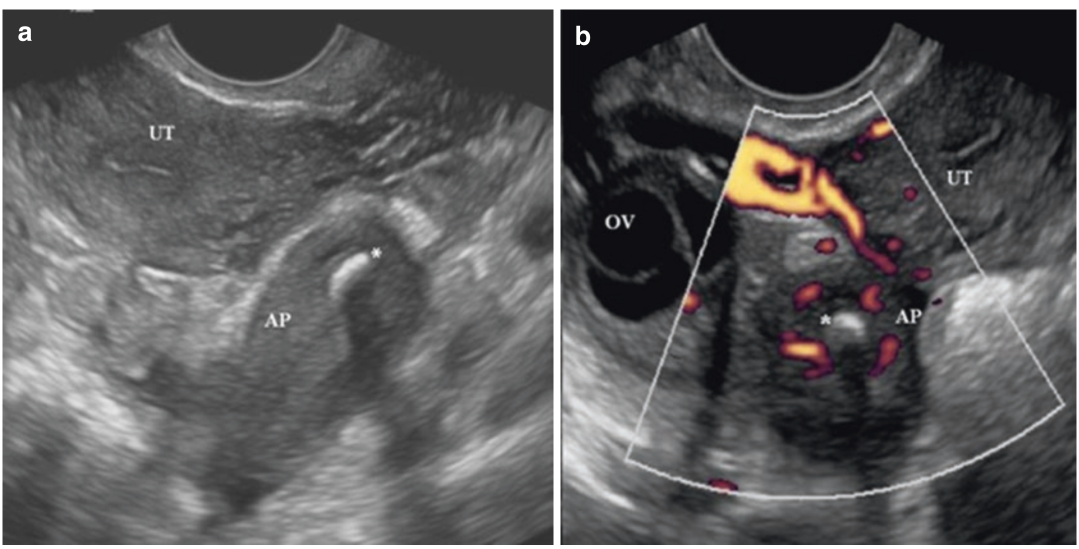

Fig. 1.10 Transvaginal imaging of the right adnexa demonstrating appendicitis. (**a**) Enlarged appendix (AP) with appendicolith (*). The uterus (UT) is also seen. (**b**) Hyperemic appendix (AP) visualized in transverse, appendicolith (*), right ovary (OV), and uterus (UT) seen. Reproduced with permission from [176]

Doppler sonography can produce high intensities and should be used judiciously, keeping the exposure time and acoustic output to the lowest level possible [177]. Transvaginal Doppler sonography is used for defining adnexal torsion or vascularized tumors. In nonpregnant women, 24% of patients with AA were diagnosed only by transvaginal scanning when transabdominal was negative [175]. Some recommend transvaginal sonography as the first ultrasound diagnostic tool for female patients with low abdominal pain [176].

1.7.5 Abdominal MRI

Magnetic resonance imaging (MRI) is the diagnostic modality of choice in patients for whom the risks of radiation or the potential nephrotoxicity of iodinated contrast agents is a major concern. It is most useful for evaluating pregnant patients with acute pain in the RLQ thought secondary to an extrauterine cause, such as AA or ovarian torsion [178, 179]. Therefore, it is prudent to perform an MRI in pregnant patients only when ultrasound findings fail to establish a diagnosis. Indications for MRI are:

- The appendix is not visualized by abdominal ultrasound.
- No other cause of an acute abdomen is found.

The MRI criteria for AA include (Fig. 1.11):

- Appendiceal diameter >7 mm
- Appendiceal wall thickening >2 mm
- Appendicolith
- Signs of periappendiceal inflammatory changes (periappendiceal fat stranding and fluid)

The MRI criteria that exclude AA are (1) an appendix of less than 6 mm in diameter and (2)

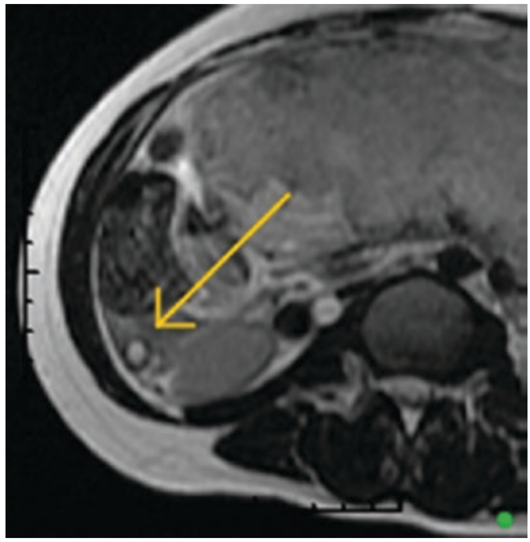

Fig. 1.11 Axial T2-weighted image demonstrating dilated appendix (*arrow*) consistent with acute appendicitis. Reproduced with permission from [180]

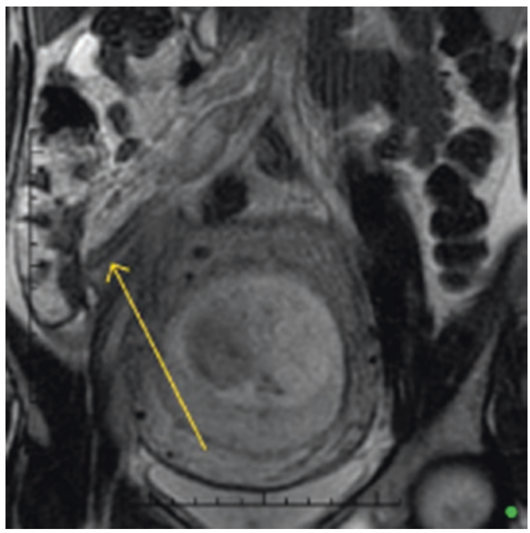

Fig. 1.12 Coronal T2-weighted image demonstrating normal appendix (*arrow*) in a 14 week gestation patient. Reproduced with permission from [180]

an appendix with a diameter of 6–7 mm with no evidence of periappendicitis (Fig. 1.12). The second MRI scenario warrants close clinical follow-up.

In pregnant patients suspected to have AA, MRI sensitivities and specificities are 80–100% and 93–98%, respectively, when compared to surgical pathology [87, 180–189]. There are

several advantages of MRI for suspected AA in pregnancy:

- Reduced rates of both negative laparotomy and perforation [185, 189]
- Identification of alternative causes for abdominal pain [187, 189, 190]
- More frequent discharge from the emergency department [185]
- Shortened length of stay in nonoperated and operated groups [185]

Abdominal MRI has a 100% negative predictive value when the appendix is visualized [184, 188, 189]. When appendix is not visualized on CT, other findings consistent with AA such as abscess formation and fat stranding often exist [191]. Although comparable studies of nonvisualized appendix on MRI have not been performed, the diagnostic performance of CT and MRI in the evaluation of AA during pregnancy has yielded similar results [183, 192]. However, some advantages of MRI over CT include the following [187]:

- Reduced requirement for contrast administration.
- An entire abdomen can be viewed in more planes.
- No radiation exposure.

MRI is not free of theoretical risks which include (1) the potential biological effects of the static and time-varying magnetic fields, (2) the heating effects of the radiofrequency pulses (>1.5 T), and (3) the acoustic noise generated by the spatial encoding gradients [178]. However, there are no reports of adverse effects from MRI during pregnancy on the developing conceptus [193]. Therefore, MRI is currently preferred over CT [194].

There are also some limitations. The patient should be informed that there are no known harmful effects from the use of MR imaging at 1.5 T or lower magnetic field strengths [178] and that there is a lack of experience with the use of field strengths greater than 2.5 T and they should be avoided at present [178]. Absolute contraindications for MR include [146]:

- Metal implants not made of titanium
- Metal implants of unknown composition
- Gadolinium administration during the first trimester

Gadolinium-based MR contrast agents are known to pass through the placenta to the fetal circulation. The contrast material is then excreted by the fetal kidneys into the amniotic fluid where the agent can remain for an indeterminate amount of time. To date, no large, well-controlled studies have been performed to document the presence or absence of adverse fetal effects resulting from maternal gadolinium administration. Therefore, the potential risks to the fetus remain unknown [146]. Rapid-sequence MRI is preferable to conventional MRI because of the briefer exposure [195].

> Informed consent should be signed by patient; the safety of MRI for the fetus has not been proved (US FDA guidelines and the *American College of Radiology*)

1.7.6 Abdominal CT

Clinicians may not be well informed of the facts relating to the use of diagnostic radiological studies in pregnancy. Lack of understanding of radiation effects on the fetus causes unnecessary anxiety in pregnant patients exposed to diagnostic radiation and may lead to unnecessary pregnancy termination. A study from 2004 examining physician perceptions of teratogenic risk associated with undergoing plain radiography and CT during early pregnancy found that 3% of the family practice physicians would recommend pregnancy termination after first-trimester CT and 0.5% following radiography in the first trimester; 12% were not sure of the need for pregnancy termination after radiography; and 19% were not sure about a CT scan examination. The same study reported that 8% of obstetricians would have recommended pregnancy termination after first-trimester CT scan examination [196].

CT scans of the appendix are identified as positive for AA if following changes are found (Fig. 1.13):

- Enlarged appendix (maximum diameter >6 mm)
- Periappendiceal inflammatory changes (fat stranding, phlegmon, fluid collection, and extraluminal gas)

Fig. 1.13 Transverse sections of an oral and intravenous contrast-enhanced CT scan demonstrate a thickened appendix and periappendiceal fat stranding (*arrow*) in a 27-week pregnancy and proven acute appendicitis. Reproduced with permission from [197]

In all instances, the "equivocal" readings influence on the sensitivity and specificity of CT, depending on how these readings were handled. It is preferable to use the multidetector row CT scan with the high-speed mode in pregnant patients since it has half the radiation dose of the high-quality mode and its scanning parameters are otherwise identical. Radiation exposure in these settings is 300 mrad, which is below an accepted safe level of radiation exposure in pregnancy of 5 rad. The current opinion is that radiation may increase the background incidence of cancers before the age of 20 by 0.06% per rad delivered to the fetus [198, 199]. These are the results from 15 to 20 years ago. Consequences of newer CT modules with lesser radiation will be evident in the next decades. Table 1.5 shows potential dose-dependent radiation effects during fetal development. Sensitivity and specificity in a pregnant population with AA are similar to the general population with values almost reaching 100% [197, 200, 201]. Limitations include a small number of patients, retrospective studies, and studies performed in tertiary care institutions; therefore, these findings may not be universally applicable. CT established a diagnosis in 30% of cases with an initial negative ultrasound scan proving the accuracy of CT as well as its superiority over sonography for this indication [201]. The higher the degree of appendiceal inflammation, the higher the sensitivity for detecting AA in pregnancy [202]. Abdominal CT delineates other

Table 1.5 Summary of potential in utero-induced radiation effects

Conception age	<50 mGy	50–100 mGy	>100 mGy
Prior to conception	*None*	None	None
1st–2nd week	*None*	Probably none	Possible spontaneous abortion
3rd–8th week	*None*	Potential effects uncertain and too subtle to be clinically detectable	Possible malformations increasing in likelihood as dose increases
9th–15th week	*None*	Potential effects uncertain and too subtle to be clinically detectable	Risk of diminished IQ or of mental retardation, increasing in frequency and severity with increasing dose
16th–25th week	*None*	None	IQ deficits are not detectable at diagnostic dose
>25th week	*None*	None	None applicable to diagnostic medicine

Reproduced with permission from [146]

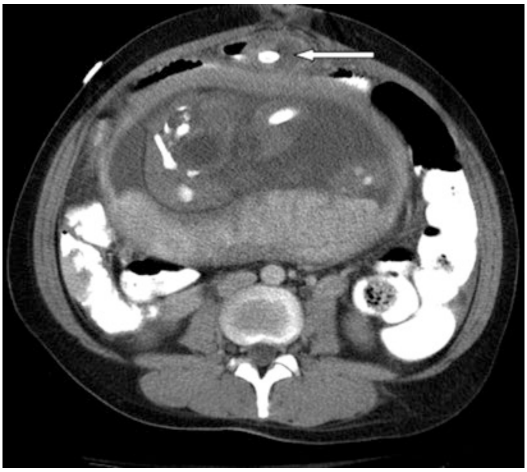

Fig. 1.14 Abdominal CT with i.v. contrast demonstrates a fluid-filled collection under the umbilicus containing an enterolith in addition to an intrauterine pregnancy in a 29-week-gestation patient. Reproduced with permission from [124]

conditions in patients with clinical presentation of AA. One of these is MD (Fig. 1.14).

The simplified diagnostic algorithm is presented in Fig. 1.15.

> Abdominal CT scan should be used when there is an uncertain clinical diagnosis or equivocal laboratory or ultrasound findings or where access to MRI or MRI expertise is limited for diagnosis AA in pregnancy.

1.8 Treatment

Let us return to our ideal; early operation is the only safe practice.

John Benjamin Murphy, 1916

Get in and get out quickly.

Joseph Bolivar DeLee, 1921

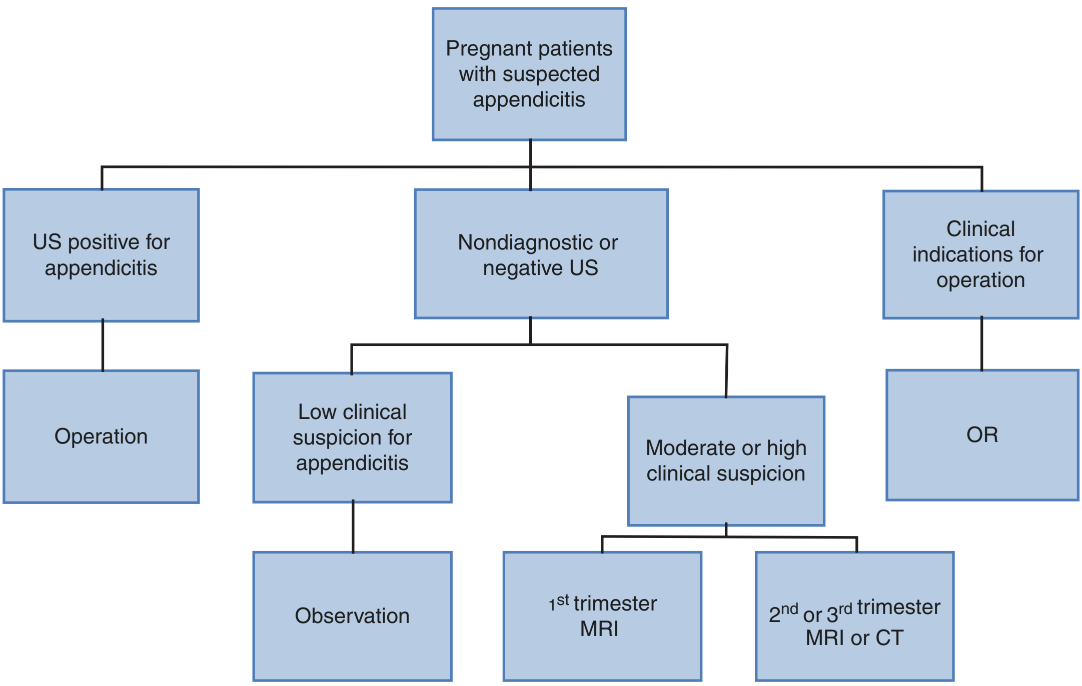

Fig. 1.15 Algorithm for the evaluation of pregnant patients with suspected acute appendicitis. Reproduced with permission from [173]

1.8.1 Conservative Treatment

If the diagnosis of AA is highly suspected or confirmed, management is always surgical removal of the inflamed appendix. Murphy's statement from 1916 was for AA in general population but should be adopted also for pregnant women. The largest population-based study on more than 7100 appendectomies in pregnancy showed that treatment was considerably different in pregnancy. Conservative management was more common in pregnancy than expected and ranges 5.8–9% [32, 203]. The first successful attempt of conservative treatment dates back in 1893 by Petersen during puerperium [2]. The idea of conservative management is to localize the process with interval appendectomy later in the pregnancy or postpartum [204]. During the active disease, ultrasound- or CT-guided drainage can be performed [205]. The lengthy symptom course should be expected [205].

If the patient is in active labor and delivery is imminent, the operation may be delayed for a short time (until the placenta is delivered), but immediate appendectomy is advised if prolonged labor is anticipated [34, 38]. The current recommendation is that surgery should be preferred to nonoperative approach [203].

1.8.2 Open Appendectomy

Because of the unreliability of the clinical diagnosis of AA in pregnancy, an aggressive surgical approach (Fig. 1.16) has been advocated to avoid progression to appendiceal perforation, which has been associated with a high rate of fetal demise [206–208].

During the 1950s, perforation of AA occurred two to three times more frequently in pregnancy [209]. In more than 7100 appendectomies during pregnancy in the United States, 60% were managed by laparotomy, 31% were managed by laparoscopy, and the remaining 9% were managed medically [210]. In Taiwan (2005–2010), OA was performed in 76% of pregnant patients [203]. Several incisions could be used.

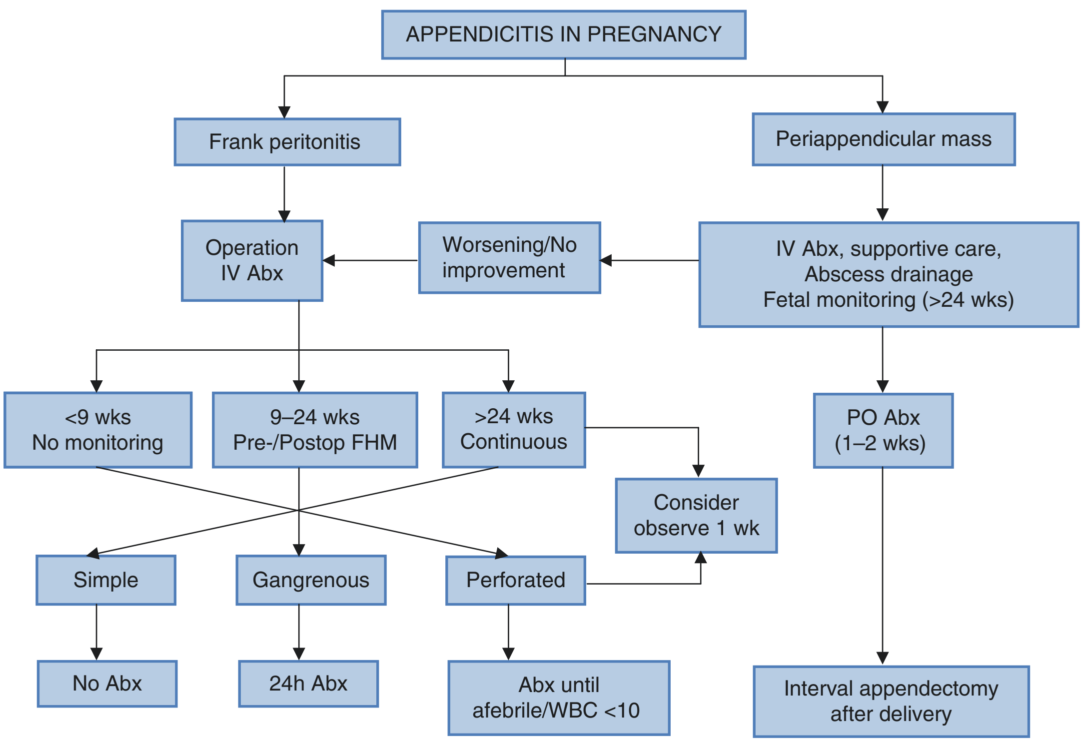

Fig. 1.16 Treatment algorithm for acute appendicitis during pregnancy. *IV* intravenous, *PO* per oral, *Abx* antibiotics, *wks* weeks, *FHM* fetal heart monitoring, *WBC* white blood cells

- The operation should be completed with minimal or no uterine manipulation which increases the risk of postoperative uterine contractions [211].
- The most experienced abdominal surgeon available should perform the procedure to shorten the operative and anesthesia time [212] and reduce possible intra- and postoperative complications.

1.8.2.1 Muscle Splitting Incision (McBurney's Incision, Gridiron Incision)

This is the incision of choice for the open approach in both general and pregnant patients. The advantages are:

- It can be performed throughout the pregnancy regardless of the gestational age.
- Direct access to the suppurative process without spreading it in clean areas.
- Minimization or elimination of uterine manipulation.
- (Mostly) small incision with extremely low risk for acute disruption or late postoperative hernia.

There are some disadvantages of this approach. In the latter pregnancy, the incision could be positioned above McBurney's incision and slightly lateral because of possible displacement of the appendix in the RUQ [8]. This change of the location of the incision is not confirmed, and the appendix can be easily located in 94% of the incisions made through McBurney's point and in 80% of the incisions made above McBurney's point [71, 213]. Another disadvantage is that it may increase the possibility of extending the incision and the necessity of uterine manipulation to secure the surgical field.

To assuage or prevent compression of inferior vena cava after 24 weeks of pregnancy, it is advisable to place a small but rigid pillow under the patient's right buttocks to tilt the uterus to the left. It can be used from the early pregnancy, as in general population, to bring closer the ileocecal segment to the abdominal wall.

Uterine Injury

Uterine injury can occur during both OA [214] and LA [215]. Incision through complete thickness of uterine wall can lead to significant complications: (1) bleeding from the incision site, (2) leakage of amniotic fluid, (3) the contamination of amniotic fluid with the purulent or feculent material, and (4) maternal CO_2 embolism during CO_2 insufflation of intrauterine cavity [216, 217]. During the operation, the ultrasound should be performed to determine the presence of a fetal heart rate and an impression of residual amniotic fluid volume. With a live fetus and enough amniotic fluid and no significant bleeding, the gestation could continue. The risk of chorioamnionitis is addressed by the use of perioperative broad-spectrum antibiotics. The immediate risk of preterm labor is addressed by the use of indomethacin (see Chap. 23), although a calcium channel blocker is also an option and would not affect amniotic fluid volume or potentially mask an infection. CS prior to the onset of labor is recommended to minimize the risk of uterine rupture [218]. If significant leakage occurs or there is a dilemma about fetal vitality, the baby should be delivered by CS during the same operation. Corticosteroids for fetal maturation could be instituted if CS is expected in near postoperative period. To detect chorioamnionitis in early phase, once or twice daily WBC and CRP could be measured. Cardiotocography should be performed on a daily basis.

1.8.2.2 Lower Midline Laparotomy

This incision is used when acute abdomen with diffuse peritoneal irritation is present. This is important for three main reasons [40]:

- Dealing with unexpected surgical findings
- Completion of “difficult” appendectomy started through other incisions or laparoscopy
- CS performed through the same incision if necessary

If CS is not indicated, then there are several disadvantages of midline and paramedian incisions:

- Difficulty of access
- Much pressure and handling of the uterus to reach the appendix
- Increased rate of abdominal wall dehiscence in near term pregnancy and labor due to increased intra-abdominal pressure
- Increased rate of a postoperative hernia in operations performed in near term pregnancy due to increased intra-abdominal pressure

The largest population-based study on over 7100 appendectomies in pregnancy showed that the rate of laparotomy was doubled compared with the nonpregnant population [32].

1.8.2.3 Right Transrectal/Pararectal/Paramedian Incision

In 1902 right transrectal incision was favored by Donoghue [219]. He stated that it is easy to reach the appendix, the incision is easy to enlarge without cutting the muscle fibers, and, in healing, there is a constant tendency of the rectus fibers to close the opening. If the incision is properly closed, there will be little danger of rupture before, during, or after delivery.

Currently, these incisions are rarely used. If the diagnosis is certain, then McBurney's incision is made. If acute abdomen with diffuse peritoneal irritation is present, then midline vertical incision is a better option. Previously (especially before the era of ultrasound), when the diagnosis between acute cholecystitis and AA was not clear, then the right transrectal incision was also diagnostic. When the appendix was found to be normal, the incision was extended cranially and cholecystectomy performed. McCorriston suggested using a right paramedian incision when the diagnosis was uncertain [220].

1.8.3 Laparoscopic Appendectomy

Some recommend the routine use of nasogastric tube due to both increased intra-abdominal pressure and pregnancy-related gastric stasis [221].

1.8.3.1 Trimester

Previously LA during the latter part of the second and the third trimester was controversial. Several case reports and small series have reported success during all trimesters without complications [143, 222, 223], but in the same institutions, there is a higher percentage of OA during the third trimester [143]. Currently, more and more LAs are done even in the third trimester [224].

When LA was introduced in pregnancy, operation times were approximately 50% longer but with decreased length of hospital stay [225, 226]. With increasing number of LAs performed worldwide, the duration of OAs and LAs became the same [143]. Currently, the mean operative times are around 45 min [227, 228], with longer operating times with advanced gestational age [228]. This is faster than the recently reported median operating time for LA in a nonpregnant population (median 60 min) and may reflect the fact that the LA in pregnancy is usually performed by experienced surgeons [228, 229]. There is no significant difference in the rates of intraoperative complications, fetal loss, or preterm delivery between trimesters [228, 230] or between OA and LA [229]. A potential disadvantage of LA compared to OA is the necessity of general anesthesia and compared only to median laparotomy is the inability to perform CS—new incision is needed.

There are many advantages of LA. Laparoscopy expands the ability to explore the abdomen with less uterine manipulation [231]. Further, it increases the ability to locate and treat dislocated appendix and results in relatively small incisions compared with the open technique or helps in detecting other unexpected causes of acute abdomen [143, 232–234]. In the case of gynecologic disease, sometimes neither insertion of additional trocars nor extension of the incision is required [229]. Reduced cecal manipulation during LA with less cecal trauma causes earlier restore of large bowel function and earlier passage of the first flatus and first postoperative stool. With open (Hasson) technique for the first trocar placement, there is almost no possibility of injury to intra-abdominal organs. Direct uterine injury during trocar placement has

been reported but without a fetal loss [216]. In addition to the general advantage of smaller incisions, less postoperative pain, and earlier return to normal activity, lower rates of abdominal wall dehiscence or herniation during labor are another potential benefit. Rapid return to full activity could reduce the frequency of maternal thromboembolic events, which can be a source of increased maternal morbidity and mortality. Thromboembolic events are more common in pregnancy [233, 235, 236]. Some found significantly shorter hospital stay in the LA group [143], while others did not find the difference [229, 237]. This can be explained by the fact that the LA group is kept hospitalized for fetal surveillance and not because of surgical need per se [237]. A Swedish study (1973–1993) evaluated 2233 LA and 2491 OA cases from two million deliveries [238]. Outcomes evaluated birth weight, gestational duration, intrauterine growth retardation, congenital malformations, stillbirths, and neonatal deaths with no statistically significant differences comparing the LA and OA group. It appears that there was an increased risk for infants in both laparoscopy and laparotomy groups to weigh less than 2500 g, to be delivered before 37 weeks, and to have an increased incidence of growth restriction compared with the total population [238]. Meta-analysis from 2012 concluded that available low-grade evidence suggests that LA in pregnant women might be associated with a greater risk of fetal loss [239]. There is no difference between LA and OA if the studies by McGory et al. [211] and Walsh et al. [228] are excluded due to many proven study limitations. Current studies show benefit from LA compared to OA [237].

> *Laparoscopic appendectomy may be performed safely in pregnant patients with suspicion of appendicitis. Laparoscopic appendectomy can be performed safely in any trimester and is considered by many to be the standard of care for gravid patients with suspected appendicitis.*
>
> SAGES clinical practice guideline (2009 and 2011)

1.8.3.2 Pneumoperitoneum

Laparoscopy during pregnancy potentially exposes the fetus to risks from (1) trocar placement, (2) the effects of CO_2 on the developing fetus and the long-term effects of this exposure with the significant fetal loss, and (3) consequences of the increased intra-abdominal pressure on the fetus (see Chap. 23).

The recommendation is that pneumoperitoneum should be carried out using an open (Hasson) technique for entering the abdominal cavity under direct vision. Another possibility is to use a Veress needle which can be inserted in either the left or the RUQ in the midclavicular line approximately 1–2 cm below the costal margin (*Palmer's point*). Some claim higher risk of perforation of intra-abdominal organs or pneumoamnion especially in advanced pregnancy [215, 226]. An optical trocar (under direct vision) can be used for entering the abdomen after pneumoperitoneum created by Veress needle as in bariatric surgery. Optical trocars can be used even without pneumoperitoneum.

Gasless Laparoscopy

In an attempt to overcome the potential adverse effects of pneumoperitoneum on the fetus, gasless laparoscopic surgery (GLS) has been developed. GLS in pregnancy has comparable outcomes to conventional CO_2 laparoscopy, but it is associated with some advantages. Hypercarbia and increased intraperitoneal pressure due to CO_2 insufflation are avoided. Literature search up to 2013 did not find any case of GLS appendectomy during pregnancy [240].

1.8.3.3 Laparoscopic Technique

In the first and early second trimesters, the technique is similar as in nonpregnant patients. The third trimester poses additional difficulty mainly because of the diminished working space available due to the enlarging uterus, the risk of injuring the uterus, and the perceived risk for excessive manipulation of the gravid uterus leading to preterm labor. In an advanced pregnancy, the port positions are somewhat different (see further

text). The patient is placed supine on the operating room table. Restraining straps are placed across the chest and thighs, and sequential pneumatic compression devices are placed on both lower extremities. Some recommend a Foley catheter [241] and a nasogastric tube placement and removal at the end of the operation. A prophylactic antibiotic is administered intravenously 30–60 min before the skin incision. Maternal end-tidal CO_2 is monitored and should be controlled within the physiological range (30–40 mmHg).

Patients are tilted to the left to displace the uterus from the inferior vena cava and to remove the small bowel from the operating field and a slight Trendelenburg position, if necessary. The procedure is performed using three ports, and their placement is modified in accordance with gestational age. In the advanced pregnancy, the first port for laparoscope (5 or 10 mm) is placed 2–4 cm cephalad to the gravid uterus in the upper midline between the umbilicus and xiphoid process. The bigger the uterus, the more cranial the first trocar is placed for easier intraperitoneal manipulation.

There are several modifications of trocar sites and trocar size depending on the laparoscopic technique and equipment. Some recommend the second port (5 or 12 mm) to be placed laterally in the RLQ and the third port (5 or 10 mm) in the RUQ in a more cranial location. When the linear cutting stapler is used for the transection of the appendix at its base, 12 mm port is necessary [242]. Other combinations of trocar placement are presented in Fig. 1.17 depending on the degree of uterine enlargement [241].

Sometimes the problems could arise with the evacuation of infected liquid in the recto-uterine pouch, especially during the advanced second or third trimester. It is difficult to reach the pouch without manipulations of the uterus, and it is important to eliminate infective fluid for two reasons: (1) to avoid pelvic abscess formation and (2) to eliminate the possibility for uterine irritability with its consequences (see Chap. 23).

1.8.4 Perioperative Considerations

See Chap. 21.

1.8.4.1 Prevention and Treatment of Preterm Labor

See Chap. 23.

1.8.4.2 Pathohistological Examination

All the extracted specimens should be sent to pathohistological examination because, in this pregnant patient group, other pathologies other than AA (including carcinoid tumor and appendiceal adenocarcinoma) could be found [143]. There is even a case of intussusception of the appendix mimicking AA [243].

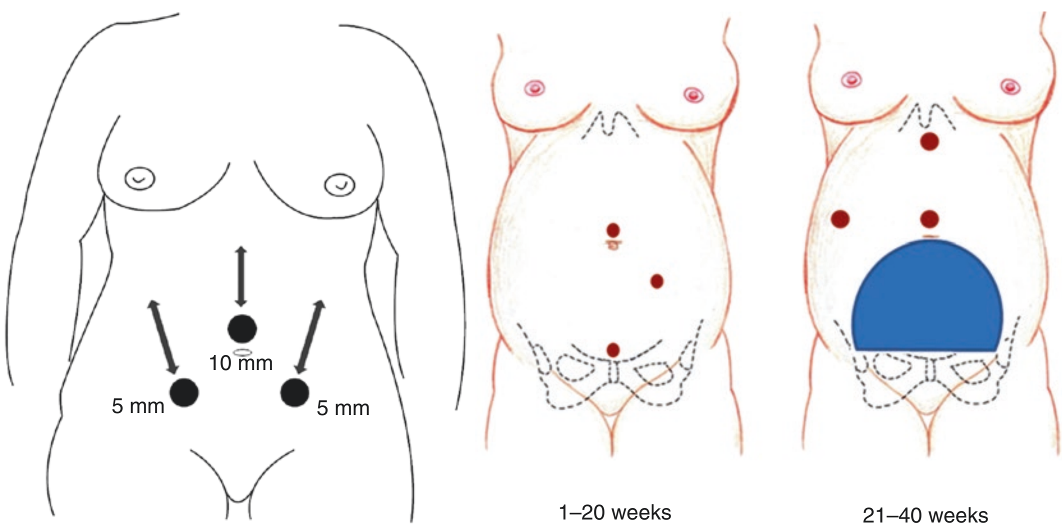

Fig. 1.17 Different trocar positions for a laparoscopic appendectomy in different stages of pregnancy. Modified with permission from [236, 241]

Pregnancy complicated with appendiceal endometriosis (AE) is a rare condition ranging 3–8/10,000 deliveries [244], and only 18 cases of AE mimicking AA in pregnancy are published (Table 1.6). Hematoxylin–eosin shows AA, and the appendiceal wall has foci of endometrial implants with acute inflammation. A panel of immunohistochemical stains, including

Table 1.6 Summary of cases of appendiceal endometriosis presenting as acute appendicitis during pregnancy and puerperium

Author	Age (years) Gravidity/ parity GA (weeks)	Symptoms and signs	WBC count per µL	Surgery	Pathology
Bogatko [295]	32; 2; 20	RQL pain, $t = 37.2$ °C	12,000	McBurney's incision	Serosal endometriosis
Lane [303]	34; 12; NS	NS	12,000	NS	Decidual reaction
Tedeshi [304]	30; 2/3; 12	NS	NS	NS	Decidual reaction
Finch [305]	28; NS; NS	NS	NS	Laparotomy	Decidual reaction, inflammation
Cutait [306]	26; 1/0; 12	RQL pain, $t = 37.5$ °C	Leukocytosis	–	Decidual reaction, inflammation
Pigne [244]	28; 2/1; 19	RQL pain, $t = 37.5$ °C	NS	Laparotomy	Endometriosis, decidualization
Gini [307]	23; 1/0; 35	RQL pain	NS	Laparotomy	Perforation, decidual formation in all three layers
Nielsen [308]	NS; NS; term	NS	NS	NS	Perforation, decidual reaction
Nakatani [309]	25; 2/0; 26	RQL pain, $t = 37.8$ °C	16,000	Laparotomy	Perforation, decidual cells and glands in all three layers
Silvestrini [310]	28; 2/1; 21	RQL pain, diarrhea	Leukocytosis	Laparotomy	Appendiceal endometriosis, decidual polyp
Stefanidis [311]	27; 3/2; 20	RQL pain, $t = 37.5$ °C	15,600	Laparotomy	Endometriosis with seromuscular involvement
Perez [245]	21; 3/1; 12	RQL pain	14,700	Laparotomy	Endometriosis with stromal decidualization
Giorgakis [300]	35; NA; 27	RLQ pain, $t = 38$ °C	Leukocytosis	Paramedian incision	Endometriosis, decidualization
Dimitriadis [312]	22; 2/1; 27	RQL pain, afebrile	13,100	Laparoscopy	Endometriosis ,decidualization
Löfwander [313]	27; 1/0; 35	RLQ pain, $t = 38$ °C	22,000	C-section with appendectomy	Endometriosis, decidualization
Faucheron [314]	28; NS; 27	RLQ pain, $t = 37.5$ °C	19,000	Pararectal incision	Endometriosis, decidualization
Packeisen [315]	32; 2/NS; 36	RQL pain	14,700	C-section with appendectomy	Endometriosis, decidualization
Dogan [316]	30; 1/0; 24	RLQ pain, $t = 37.3$ °C	19,500	Paramedian incision	Endometriosis, decidualization
Lebastchi [317]	33; NS; 31	Upper abdominal pain, afebrile	18,700	Laparotomy	Endometriosis, decidualization
Collom [318]	32; NS; 34	RLQ pain, $t = 38.3$ °C	12,100	Laparoscopy	Endometriosis, decidualization
Balta [319]	33; 1/NS; 29	RLQ pain, $t = 37.2$ °C	16,700	McBurney's incision	Endometriosis, decidualization
Murphy [320]	31; 2/1; 18	RQL pain, afebrile	11,600	Laparoscopy	Endometriosis, decidualization
Garcia [321]	NS	NS	NS	NS	NS

GA gestational age, *NS* not specified, *RQL* right lower quadrant

cytokeratins CK_7 and CK_{20}, estrogen receptor, and CD_{10} and PAX8, can differentiate that the intramural glands and the appendiceal mucosa are of different nature, as the former react as endometrial mucosa, whereas the latter react as a colonic-type mucosa [245]. Cytoplasm positivity of valentine and the nuclear presence of progesterone receptors along with the lack of pan-cytokeratin, HMB-45, and calretinin are characteristics for deciduosis. A decidual polyp, which occludes most of the appendiceal lumen, is the extremely rare cause of AA during pregnancy.

1.8.4.3 Postoperative Course

Potential advantages of LA in the pregnant patient include decreased fetal depression due to lessened postoperative narcotic requirements, lower risks of wound complications, and diminished postoperative maternal hypoventilation (see Chap. 21). A nasogastric tube is extracted after the operation and early ambulation started after several hours. Oral intake of fluids should be commenced within the initial 12 h of operation if there are no nausea and vomiting.

1.9 Specific Considerations

1.9.1 Normal Appendix

1.9.1.1 Incidence

NARs during pregnancy and through decades vary considerably (4–55%) [8, 11, 12, 17–24, 26, 27, 152, 171–173, 222, 241, 246–250]. Between 1951 and 1973, the AA was confirmed in 58–68% [152, 248–250]. In comparison, NAR in the general population ranges 10–15% and as high as 26% among the reproductive-age females. It should be stressed that NA does not mean negative exploration. Around 15–20% of patients with normal appendix have another pathology (e.g., ovarian cyst, ovarian torsion, mesenteric adenitis, fibroids, and salpingitis) as the cause of the abdominal pain [173]. The difference in the NAR could be explained by differences in the rate of imaging assessment prior to surgery. The combination of physical examination, ultrasound, and CT has the lowest NAR [171]. NAR with clinical evaluation only is 54%, 36% in the clinical evaluation and ultrasound group, and 8% in the ultrasound and CT scan group [171]. Recent studies without the use of abdominal CT have a lower incidence of NAR (11% and 16%, respectively) [71, 236]. With increased use of abdominal CT, the NAR declines without the cost of higher perforation rate but with the additional risk of radiation consequences.

High NAR may be due to the surgeon's propensity for early intervention to prevent perforation and avoid unnecessary morbidity and mortality. The highest rate is during the second trimester [43]. Obstetric complications due to the abdominal operation are the rarest in the second trimester. Therefore, surgeons could use exploration in the second trimester more liberately. There is a decreased risk of NAR in the puerperium. This indicates that puerperal women experience abdominal pain less frequently or are less prone to seek care for abdominal pain [43]. Additionally, clinicians use abdominal CT more liberately in puerperium because there is no radiation exposure to the fetus. There is no significant difference of NAR between laparoscopic and open appendectomy (OA) groups [241]. Probably, as in nonpregnant population, the correlation between NAR and perforation rate exists. In one older study, NAR was 28.5% and perforation rate 20% [8]. Unfortunately, NA is not without the risks. The fetal loss rate of 2–3% for both NA and nonperforated AA is reported [211, 251]. It is not known whether it is the type of the procedure or undetected underlying pathology that influences fetal risk rates. Therefore, clinicians should consider three issues: (1) the accuracy of preoperative diagnosis, (2) delay to surgery, and (3) radiation risks for the fetus.

It should be noted that using modern diagnostic modalities, correct diagnosis of the acute abdomen during pregnancy depends on the cause.

It can be also presented as an *index of wrong diagnosis and can be compared with other acute conditions in pregnancy*:

> *Index of wrong diagnosis* (%) = provisionally diagnosed cases − confirmed cases × 100 provisionally diagnosed cases

Up to the more routine use of abdominal MRI or CT scan, it was up to 50% [37] and was trimester dependent (18% in the first, 37% in the second, and 39% in the third [24]). For comparison index of the wrong diagnosis is only 8.5% for acute cholecystitis [20, 252]. Wrong diagnosis of AA between 1951 and 1973 was 32–42% [152, 249, 250]. In two studies published in 1953 and 1954 analyzing the previous decade, the index of the wrong diagnosis was 56–65% [65, 80].

1.9.1.2 Indications for Appendectomy

There is still a dilemma to perform or not an LA if the appendix looks macroscopically normal in the nonpregnant patient, as well as among the population with no other abdominopelvic pathology. Previous reasons were:

- Retaining a normal-looking appendix allows it to be used in reconstructive procedures [253].
- 43% incidence of spontaneous abortion after OA [249].

Probably this higher rate of spontaneous abortion was due to the manipulation of the uterus precipitating uterine irritability and subsequent abortion or labor.

Others recommend the removal of the appendix: (1) to rule out AA histologically and (2) to eliminate the differential diagnosis of AA if the patient's symptoms return. It can partly be explained by the fact that gross changes are not visible if intramural, mucosal, and submucosal changes in the appendix are present which could be responsible for the symptoms. Van den Broek et al. reported that 9% continued to have recurrent RLQ pain after negative laparoscopy without appendectomy [254]. This is due to early intraluminal (mucosal) inflammation—endoappendicitis—which subsequently leads to transmural inflammation, or the inflammation subsides and could lead to chronic appendicitis with recurrent episodes of RLQ and other symptoms mimicking AA. Several studies report 20–22% of patients with clinical suspicion of AA who underwent appendectomy responded very well to appendectomy in spite of a normal microscopic examination of the appendix. The explanation could be found in other underlying causes such as appendix colic, appendiceal fecalith, and functional appendiceal abnormality or functional appendicopathy that might be the contributory factors rather than acute inflammation [255, 256]. In one study, there were 30% of intraoperative diagnoses of normal appendix confirmed with inflammation confirmed histologically. Authors recommend appendectomy in these situations [257]. These conclusions are similar to SAGES guidelines for LA in general population (04/2009): *If no other pathology is identified, the decision to remove the appendix should be considered but based on the individual clinical scenario. Macroscopically normal appendices may have abnormal histopathology. Several studies have shown a 19–40% rate of pathologically abnormal appendix in the setting of no visual abnormalities. Therefore, the risk of leaving a potentially abnormal appendix must be weighed against the risk of appendectomy in each individual scenario.*

Furthermore, some neoplasms of the appendix can occur in an organ that appears grossly unremarkable. If pseudomyxoma peritonei is observed, the appendix should always be removed and subjected to a thorough histological examination.

> As a surgeon, you should not be deterred from removing an appendix once the diagnosis is suspected because pregnancy is not affected by the removal of a normal appendix [258].

1.9.2 Incidental Meckel's Diverticulum

Given the high incidence of perforation (57%) resulting in significant maternal and fetal mortality, removal of incidentally found MD is justified in the pregnant patient [123], especially (1) in patients with desire for future pregnancies and (2) due to specific diagnostic difficulties of the condition in pregnancy.

Benefits from the removal of an incidental MD in general population are far superior to the risk of developing complications. If the patient in general population fulfills any of the following criteria (or combination), then there is an indication for the incidental MD to be removed [259]:

- Patient age younger than 50 years
- Male sex
- MD length greater than 2 cm
- Ectopic or abnormal features within a diverticulum

When one criterion is met, the overall proportion of symptomatic MD was 17%. When two, three, or all four criteria were met, the proportion increased to 25%, 42%, and 70%, respectively [259]. If the asymptomatic MD or symptomatic MD is found, *diverticulectomy* or *wedge small bowel resection* with subsequent bowel continuity is performed both during OA and LA. During LA an endoscopic linear cutting stapler is introduced through a 12 mm trocar and applied to the base of the MD, perpendicular to the base of the MD but transverse to the longitudinal axis of the bowel. The stapler is fired and the MD resected off the ileum. Small bleeding points at the edge of the staple line, if present, are sutured intracorporeally with 3-0 resorptive sutures. All the specimens are delivered through 12 mm (which can be extended if needed) port with the use of a bag if needed. A wedge resection is not necessary for these incidental findings because the base of the MD is not inflamed. If suture techniques are used after excision, bowel continuity is achieved by placing intracorporeal sutures with 2-0 or 3-0 resorptive sutures. Specimen should always be sent for pathohistological examination.

1.9.3 Ectopic/Heterotopic Pregnancy

Ectopic pregnancies (EPs) occur at a frequency of approximately 16/1000 patients [260]. Only 24 cases of EP has been reported in conjunction with AA in the medical literature since 1960 [261–264]. One of these cases is maybe not really concurrent AA because the patient presented 1 week after termination of EP [260]. It is unknown whether AA is coincidentally associated with EP. EP may trigger AA through a combination of contiguous initial inflammation which creates a portal for infection in the appendix by normal colonic bacterial flora, the so-called periappendicitis [261]. Lymphoid hyperplasia causes luminal obstruction. A subsequent increase in intraluminal pressure results in ischemia of the appendiceal wall. In the opposite direction, an antecedent AA with spontaneous resolution could also conceivably result in peritubular inflammatory adhesions favoring the development of the EP. It is of particular interest that 75% of tubal pregnancies involve the right tube [21]. Also reported cases of concurrent EP and AA have indicated a predilection for right tubal EP (75%) versus left tubal EP (16%) [261]. The rarest form is AA with heterotopic pregnancy (HP). This is the most difficult situation because the patient has three potential causes of abdominal pain: appendix, intrauterine, and extrauterine pregnancy [265].

Although advances in transabdominal and transvaginal sonography and highly sensitive tests for βHCG have facilitated earlier diagnosis of EP before the onset of clinical symptoms, differences in operator technique and obscuring bowel and gas may render preoperative diagnosis of AA and/or EP inconclusive. A corollary of this is that lack of definitive findings on sonography (such as free pelvic fluid, echogenic adnexal mass for EP, and noncompressible appendix >6 mm with free fluid for AA), in the presence of high clinical suspicion from a complete history and physical examination, should not preclude a differential diagnosis

including AA and EP in the workup of acute abdomen in pregnancy [27, 42, 261, 265].

Because of the uncertainty in diagnosis and to improve the maternal prognosis, emergency exploration is indicated. Confirmation of the diagnosis and the management of both EP and AA may be performed by laparoscopy, either microlaparoscopy or classic laparoscopy, prior to preceding to an open laparotomy [27, 261, 266, 267], especially when the hemorrhagic shock is encountered. There are no recommendations whether to do appendectomy if the normal appendix is found during exploration with proven EP. Appendectomy could be recommended if Fallopian tube-sparing surgery is performed due to (1) not adding to postoperative morbidity and significant risk of postoperative complications, (2) further pregnancies or possible recurrent EPs which have lesser differential diagnosis if a patient presents with lower abdominal pain, (3) elimination of the possibility of AA in this high-risk group due to age and increased incidence of AA when right-sided recurrent EP is present [260], and (4) elimination of the possibility of AA which can cause periadnexal adhesions increasing the risk of right-sided EP.

1.9.4 Assisted Reproductive Techniques

1.9.4.1 General Considerations

In vitro fertilization (IVF) is now widely used for the treatment of infertility. Low birth weight and macrosomia are also known to be associated with immediate and long-term risk to offspring health, and IVF singletons are at increased risk of these complications [268, 269]. It is now recognized that factors leading to infertility may be responsible for adverse perinatal outcome rather than the process itself [270]; however, which parental characteristics of infertile couples contribute to adverse perinatal outcomes in IVF singletons and can thereby be targeted for intervention remains unknown. Maternal characteristics, in particular, maternal age, the source of the oocyte, and cervical causes of infertility are strongly associated with the risk of low birth weight and preterm delivery in singleton live births resulting from IVF. Notably, some of these associations were in the opposite direction to those seen for successful live birth. Thus, in women who successfully have a singleton live birth with IVF, the risk of low birth weight is reduced in older compared with younger women, and both low birth weight and preterm are reduced when the woman's own embryo has been used [271].

1.9.4.2 Published Reports

In cases of IVF-ET techniques, the complication of EP/HP is relatively common, occurring in 1–3% of these pregnancies [272, 273], while HP has been estimated at 1/30,000 non-IVF pregnancies [274]. Transfer of four or more embryos poses an additional risk for HP [275]. There are five cases of AA in IVF-ET pregnant patients which present significant incidence in comparison to the incidence of non-IVF pregnancies (24 cases—see Sect. 1.9.3). Of these, two cases had HP (9 weeks [267] and 6 weeks [276]). Both patients underwent right salpingectomy and appendectomy and both delivered by CS. The third case described a woman with a perforated appendix and an EP [266]. The remaining two are iatrogenic appendiceal punctuations with the needle for oocyte retrieval and subsequent development of perforated AA [277, 278]. Indicative of iatrogenic injury is the development of AA several (up to 9) days after the IVF procedure.

In patients with severe abdominal pain after both IVF and ET techniques, AA and EP should be included in the differential diagnosis [276]. During diagnostic laparoscopy, both appendix and adnexa should be always examined in IVF pregnant patient despite proven normal intrauterine pregnancy, especially if AA is proven intraoperatively with fresh blood in the pelvis or around the adnexa or appendix. Additional confirmation of this rule is that βHCG in HP is elevated due to normal intrauterine pregnancy and is not diagnostic for HP.

Appendectomy is mandatory (Fig. 1.18), and therapeutic approach of simultaneous EP/HP depends on several factors:

Ruptured HP

1. Intrauterine pregnancy preserved
2. Salpingectomy or salpingotomy

Ruptured EP

1. Salpingectomy or salpingotomy

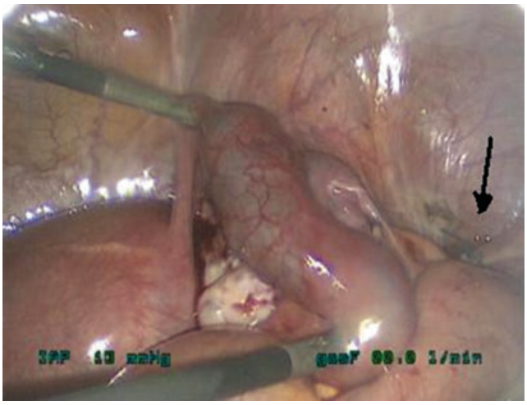

Fig. 1.18 Laparoscopic view of unruptured ectopic pregnancy in the right Fallopian tube. The knot is placed on the base of antecedent appendectomy (*arrow*). Reproduced with permission from [279]

The benefits of salpingectomy over salpingotomy are uncertain. Salpingectomy may be easier and safer, especially in the presence of a live intrauterine pregnancy. It reduces the risk of complications such as the persistent bleeding or retention of trophoblastic tissue that can occur after salpingotomy [274]. Also, if Fallopian tubes are significantly damaged and not functional for further spontaneous pregnancies, salpingectomy is recommended. Salpingectomy should be considered also if the contralateral Fallopian tube is healthy as this treatment does not preclude future fertility. For unruptured variants, therapeutic recommendations are:

Unruptured HP
1. Intrauterine pregnancy preserved
2. Salpingectomy or salpingotomy

Unruptured EP
1. Methotrexate

Even a case of ovarian hyperstimulation syndrome (OHSS) and AA is described [280]. Epigastric pain is not an uncommon symptom in patients with severe OHSS with massive ascites. Febrile morbidity is often observed in patients with severe OHSS without infection [281]. An elevated white blood cell count is also found both in patients with severe OHSS [282] and in those with AA. The possibility is raised that OHSS might affect the course of concurrent AA. An increased rate of infectious disease was reported in patients with OHSS, possibly due to immunodeficiency as a consequence of hypoglobulinemia, a frequent occurrence in patients with severe OHSS [281]. Severe stress associated with symptoms of OHSS, a hospital stay, multiple monitoring, and therapies might also impair immunoprotective status. Following this logic, it may be that AA with OHSS could be more aggressive and is likely to rupture than without OHSS. Once bacteria are seeded into the peritoneal cavity associated with OHSS, they may grow rapidly to form abdominal abscesses, because ascitic fluid of OHSS serves as an excellent culture medium for bacteria with its rich source of nutrients including albumin [283]. It seems that OHSS, if complicated by intraperitoneal inflammatory disease, may worsen its potentially life-threatening conditions.

For patients who appear to develop high-risk signs of OHSS, such as rapidly increasing estradiol levels or massive follicular recruitment, a decrease of medication dosages or alteration of the ratio of individual medications in the regimen could be attempted, but if the nonobstetric acute abdomen is suspected or proven, all these medications should be withdrawn. In the single case of OHSS with perforated AA, there is no mention of perioperative care except appendectomy and antibiotics and no mention of any complications of prolonged (37 days) postoperative course [280].

1.9.5 Sickle Cell Disease

1.9.5.1 Incidence

There is no data available regarding the incidence of AA and appendectomy in sickle cell disease (SCD) patients during pregnancy. The incidence

depends on the prevalence of SCD in different regions of the world. In Saudi Arabia, the incidence is 16.9% [284]. It is known that the incidence of AA is lower in a nonpregnant population with SCD than in the general nonpregnant population [285, 286]. Also, homozygous SCD is now known to be widespread and has broad clinical variability; therefore, conclusions are difficult to be made.

1.9.5.2 Clinical Presentation and Laboratory Findings

In the largest study [284], 75% of the SCD patients reported pain in their RLQ, the same as those reported in other studies for pregnant nonsickler patients [27]. Vomiting was a common complaint (67%) [284], and it was comparable to other reports for pregnant nonsickler patients with AA [287]. Only 50% of the AA patients had a fever, while none of the sickler patients had pyrexia in the normal appendix group. Around 75% of the AA patients with SCD had WBC >16,000/mm^3 [284]. As in other studies, there is a significant difference in the WBC counts in patients having AA compared to those with noninflamed appendices [25]. As with nonsickler patients, delaying the appendectomy beyond 24 h in their third trimester is associated with gangrene and perforation of the appendix [18, 284, 288].

1.9.5.3 Prognosis

Pregnancies in SCD patients, in general, present a clinical challenge as maternal mortality is 1–2% and perinatal mortality are 5–6% [289, 290]. Maternal mortality is rarely encountered in cases of AA in pregnant nonsickler patients [27], and there was none in largest AA study in SCD patients [284]. The fetal loss and the premature delivery rates were 9 and 18%, respectively, which are consistent with other reports [13, 19]. The incidence of complication in SCD patients in Al-Mulhim's study is lower than in other studies [291]. This may be because of the milder form of SCD in this area (Al-Hassa) due to the presence of high levels of HbF in the affected population. The high HbF levels protect against several clinical features associated with SCD, but the association between HbF levels and the severity of the disease process is complex [289].

1.9.6 Appendiceal Endometriosis/Deciduosis

1.9.6.1 Historical Considerations

Formation of ectopic decidua (deciduosis) during pregnancy is a well-documented phenomenon that has been attributed to hormonal effects on the ectopic endometrium, namely, endometriosis, or on the normal subceolomic mesothelium. AE was first described in 1860 by von Rokitansky [292], and then Hirschberg in 1905 coined the term *periappendicitis decidualis*, describing a patient with AE with right-sided tubal EP [293]. Sampson proposed the theory of retrograde menstruation as the primary etiological factor producing endometriosis [294] and reported AE. The first AA due to AE in 20 weeks of pregnancy was described by Bogatko in 1949 with the uneventful postoperative course and later delivery by CS [295].

1.9.6.2 Incidence

AE is rare in general population, occurring at the rate of 0.2–0.3% in appendectomy specimens [296]. AE accounts for 0.0075–0.045% of all cases of extrapelvic endometriosis [297] and 1% of all cases of pelvic endometriosis [298] in general population. A more recent study found the prevalence of AE in patients with biopsy proven endometriosis or with chronic RLQ pain of 4.1 and 3.7%, respectively [299]. Notably, this was higher than the 2.8% prevalence by Giorgakis et al. in 2012 and much higher than its prevalence in all patient population (0.4%) [300]. Pregnancy complicated with AE is rare, ranging 3–8/10,000 deliveries [244].

1.9.6.3 Risk Factors

When age, parity, and pregnancy duration at diagnosis were compared for women experiencing AE and AA during pregnancy, no differences were found between the groups [24, 43, 301]. When pelvic endometriosis is present, the odds ratio for the presence of AE was 20.9 compared with the general population [299].

1.9.6.4 Clinical Presentation

Isolated AE in general population is usually asymptomatic, and the lesions are discovered incidentally

in appendectomy specimens or during colonoscopy when an inverted or bulbous appendiceal orifice is noted. Cyclic RLQ pain during menstruation is typical before pregnancy. In pregnant population, the frequency of the presenting symptoms and signs such as abdominal pain, nausea, vomiting, and body temperature was not different in acute AE and AA and therefore not helpful in establishing the correct diagnosis (Table 1.6).

1.9.6.5 Diagnosis

As physical examination, WBC count was not different in acute AE and AA and therefore not helpful in establishing the correct diagnosis (Table 1.6). Leukocytosis can be due to deciduosis (or normal pregnancy) that has been related to the production of granulocyte colony-stimulating factor [302]. The only gold standard for the diagnosis of EA is laparoscopy or laparotomy, done in standard fashion for AA (see Sect. 1.9).

1.9.6.6 Prognosis

Most cases of AE are discovered as a result of an incidental appendectomy. The occurrence (of complications) is higher during the third trimester (Tables 1.6 and 1.7). This difference, however, was impossible to evaluate because of the small sample size and missing variables, e.g., the timing between diagnosis and surgery. It may be speculated that decidual reaction in pregnancy affects decidual cells present within the appendix as well. Changes in intra-appendiceal decidual cells would induce a more inflammatory response, which, in turn, may increase the risk of perforation. Perforation is probably facilitated by this transmural lesion as it occurs in the endometriotic area [314]. Around 30% of cases during pregnancy was complicated by perforation at the time of surgery; there were no maternal or fetal complications in 45% of the cases; and there was one case of preterm labor with infant death.

1.9.7 Appendiceal Carcinoid

Even in general population, tumors of the appendix are rare, and the most common is appendiceal carcinoid which accounts for 85% of appendiceal tumors [322], with a median age of 29.8 years [323]. In 80%, the appendiceal carcinoids are incidentally discovered in the removed organ without particular signs before surgery. Carcinoid tumors are found in 0.3–0.9% of appendectomy specimens in general population [324]. There are several cases of appendiceal carcinoid in pregnancy presenting as AA [325–330], the first published by Berriors et al. in 1965 [329]. The interaction between the carcinoid tumor of the appendix and the pregnancy has not yet been elucidated [327].

Table 1.7 Comparison between appendiceal endometriosis presenting as acute appendicitis in pregnancy and pregnancy complicated with classic acute appendicitis

Variable	Appendiceal endometriosis in pregnancy [245]	Acute appendicitis in pregnancy [24, 301]
Age (years)	27	27
Primiparous (%)	27	32
Multiparous (%)	45	68
First trimester (%)	36	38
Second trimester (%)	28	52
Third trimester (%)	36	10
RLQ pain (%)	73	72
Mean temperature	37.5 °C	37.6 °C
Mean WBC (mm^3)	9800	16,400

Reproduced with permission from [245]

Postappendectomy therapeutic principles during pregnancy depend on the:

- Tumor diameter (2 cm)
- Tumor localization
- Tumor grade and stage
- Weeks of gestation

If the tumor is on the appendiceal base or is greater than 2 cm, right hemicolectomy is indicated several weeks after delivery [327]. If CS should be performed due to obstetric indications, right hemicolectomy should be performed after CS during the same operation.

Selective specific medical treatment like somatostatin (analogs) and avoidance of conditions and substances that cause flushing may be useful during pregnancy [331].

1.9.8 Peritpyhlitic Abscess

When an appendiceal abscess is recognized, drainage should be established without delay because of the great liability of rupture of the abscess into the peritoneal cavity, especially in pregnancy. The explanation lies in the fact that the growing uterus during pregnancy, the contracting uterus during labor, and the shrinking during puerperium form the unstable inner boundary of the abscess, hence the great liability of the abscess to rupture [44]. The greatest possibility of this event is during labor when contracting uterus, later shrinking uterus, has a significant impact of disseminating pus with the possibility of contamination of genital tract.

1.9.9 Puerperium

The abdominal wall also undergoes significant change during pregnancy, with muscle tone reduction and skin elasticity to accommodate the enlarging uterus. The abdominal wall tone remains lax for several weeks postpartum, returning to a near-nonparous level in 6–7 weeks. The hallmarks of the acute surgical disease, abdominal guarding and rigidity, are rarely encountered during the early puerperium. This single feature is responsible for confusion and delay in proper surgical diagnosis. Some found pronounced abdominal distention and acute diffuse tenderness due to peritonitis with secondary paralytic ileus but little guarding [46, 332]. Puerperal changes in blood components may be confusing as well. During the first 10–14 days of the puerperium, WBC counts of 20,000–25,000/mm^3 are not unusual; there is also a predominant increase in neutrophils. The erythrocyte sedimentation rate may increase to 50–60 mm/h. Reliance on either the erythrocyte sedimentation rate or the WBC count for the diagnosis of acute infection may be misleading. The enlarged uterus does not hamper exposure, even in the first week. At the time of surgery, the uterine fundus is inferior to the umbilicus. There were no adhesions encountered in the CS group. The course of the procedure and recovery was identical to the remainder of patients.

The final unique consideration in the postpartum patient is the presence of a healing abdominal incision after CS. There are no published studies on outcomes for recent abdominal incisions subjected to early pneumoperitoneum. Most commonly pneumoperitoneum is limited to 10 mmHg in the CS patients. This may have been beneficial in preventing undue mechanical strain on the healing wound, though there were no controls with the standard (15–16 mmHg) for comparison. It seems prudent to utilize the minimal intra-abdominal pressure necessary for adequate exposure in these patients. Although evidence suggests fascial separation, if present, occurs early, it remains to be seen what long-term status these incisions will achieve. No hernia has developed in these patients with a follow-up of 5.5 years [333].

1.10 Prognosis

The mortality of appendicitis complicating pregnancy and the puerperium is the mortality of delay.
Edmund Adam Babler, 1908

1.10.1 Conservative Treatment

The results of the largest population-based study of more than 7100 pregnant patients with AA confirm current recommendations of appendectomy during pregnancy. Statistically, significant increase was noted in maternal morbidity including septic shock (6.3-fold), peritonitis (1.6-fold), and venous thromboembolism (twofold) with conservative treatment [32]. Risks of perinatal adverse events such as preterm labor and spontaneous abortion are significantly higher [203]. The higher maternal mortality rate is found in nonoperated pregnant patients [334]; therefore, surgical treatment with highly suspected or proven AA is recommended.

1.10.2 Perforation Rate

Perforation rate in pregnant population has been reported as high as 55–60% compared to 4–19% in general population [33, 41, 211, 225]. Delay in the diagnosis and surgical intervention can lead to appendiceal perforation. Around 1950 perforation of AA occurred two to three times more frequently in pregnancy [209]. A 66% perforation rate has been reported when the operation is delayed by more than 24 h compared with 0% when surgical management is initiated prior to 24 h after presentation [41]. The timing of intervention varies by trimester: 90% of patients in the first trimester undergo the operation within 24 h of the onset of symptoms, whereas in the third trimester, up to 64% of the patients have symptoms for more than 48 h before operation [101, 335]. Diagnostic and therapeutic delay of more than 48 h is especially seen during labor and early puerperium [46, 336–338]. In 1908, Babler collected 28 cases of AA during early (first 10 days) puerperium. The perforation rate was 64% [339]. The difficulty in making a clinical diagnosis particularly close to term combined with the previously quoted high incidences of fetal and maternal mortality for appendiceal perforation has led to a traditionally low threshold for surgical intervention. This is partly due to inaccurate preoperative diagnostic imaging. This has resulted in a higher NAR, ranging 23–55% in pregnant women compared with 18% in nonpregnant women [24, 25, 43, 149, 228, 236, 339]. The first trimester yields a greater accuracy, but more than 40% of patients in the second and third trimesters will have a normal appendix [208]. Perforation can also result in an increased risk of generalized peritonitis because the omentum cannot isolate the infection [42]. Therefore, extra caution should be applied during early puerperium because:

- Painful and prolonged labor masks the symptoms of AA.
- Epidural analgesia during labor suppresses the symptoms of AA.
- Abdominal pain affects up to 98% of postpartum women [340, 341].
- Leukocytosis and fever are especially exaggerated in the early puerperium.

The trend in overall perforation rate is lowering from 25–29% [71, 342] to 15–20% during the last several decades [22, 32]. Partly this decrease in perforation rate is due to recent findings of shorter admission to surgery interval. The perforation rate through the trimesters increases: 6–8.7%, 10–12.5%, and 13–26.1%, respectively [22, 43]. In summary, there are several causes for the treatment delay [46, 101, 234, 335, 336]:

- *Atypical clinical picture* when observation delays the intervention
- *Time delay during consultations* if departments/institutions are dislocated
- *Time delay during the patient transfer* if departments/institutions are dislocated
- Third trimester, *painful* labor, and early puerperium
- *Epidural analgesia* during labor suppresses the symptoms of AA

1.10.3 Maternal Outcome

1.10.3.1 Maternal Mortality

Since 1950, the mortality seems to have decreased partly due to the introduction of antibiotics. Before 1900, maternal mortality was 30%; with perforation operated even without delay, it was up to 58% [343, 344], while up to 100% when diffuse peritonitis was present [345, 346]. In 1908, Babler reported more than 200 cases of AA in pregnancy with a maternal mortality of 24% but 45% when diffuse peritonitis was present [339]. In 1947 Meiling claimed that maternal mortality is 0.71% when the disease is confined to the appendix, 30% when there is peritonitis, and 50% when the appendix is perforated [332]. Of even greater significance found in 1954 was that cases occurring

in the last 3 months of pregnancy showed a mortality of 20.7% [347]. Today, overall, maternal mortality is less than 1% [25–27, 42]. It is rare in the first trimester and increases with advancing gestational age [258]. For a comparison, when MD was the cause of acute abdomen during pregnancy (patients from 1949 included), maternal mortality was 17% [123]. In all mortality cases, MD perforation was found [123].

Adverse maternal (and fetal) outcomes are associated with [19, 41, 143]:

- A *delay in surgery* (>24 h after onset of symptoms)
- Appendiceal *perforation*
- Maternal temperature >38 °C
- Leukocytosis >16,000/mm^3

The degree of leukocytosis is an indicator for perforation and is rarely present if the values are below 16,000 mm^3 [101]. If the appendiceal perforation is present, maternal mortality occurs in up to 4% in contrast to less than 1% in non-perforated AA [342]. Recent studies claim 0% maternal mortality even with perforated AA [71, 249, 348]. The risk of perforation increases with gestational age due to prolonged period between admission and operation in the third trimester [42, 101]. Additional problem is that with the expulsion of the uterine contents and reduction in the size of the uterus, the abscess disintegrates, and the contents are disseminated throughout the abdominal cavity, leading to general peritonitis. Therefore, significant clinical deterioration without signs of internal or external bleeding could be observed after delivery in patients with unrecognized AA.

1.10.3.2 Maternal Morbidity

Pregnant and nonpregnant women with AA have similar composite 30-day major morbidity (3.9% vs. 3.1%, $p = 0.212$) and all specific complications except pneumonia, which occurred more frequently in pregnant women (0.7% vs. 0.2%, $p = 0.004$). Postoperative pneumonia was observed only after general endotracheal anesthesia [144]. Limited data exist about the risk of chorioamnionitis and puerperal infection.

Increased maternal morbidity associated with AA may not only be explained by the increased rate of peritonitis but also by a twofold increase in laparotomy rate [210]. Maternal morbidity with LA is the same [203] or less [237] when compared to OA. The advantages of laparoscopy include decreased surgical trauma with lesser use of analgesics especially opioid that can lead to fetal depression, decreased gravid uterine manipulation, minimal use of electrosurgery in the proximity of the uterus, earlier recovery of bowel function with shorter time to oral intake and therefore less nutritional stress to the fetus, early mobilization which may minimize the increased thromboembolic risk associated with pregnancy, shorter postoperative length of stay in hospital, and faster return to daily activities [230, 232, 241, 349–351]. OA patients have a significantly longer hospital stay [143, 203]. Similar hospital length of stay for OA and LA groups is due to the fact that the LA group is kept hospitalized for fetal surveillance and not because of surgical need per se [237]. Long-term follow-up after LA in pregnancy showed that it is safe and efficacious, without any long-term effects to the mother [352].

In the largest study with 1203 preterm deliveries due to AA during pregnancy, CS rates were similar in both pregnant populations with and without AA, which is consistent with traditional teaching that promotes CS only for obstetrical indications [210]. The degree of appendiceal inflammation does not influence the type of *delivery at term* with half of the patients having CS and another half vaginal delivery in both non-perforated and perforated groups [85]. However, the aforementioned largest study to date found that the rate of CS was almost doubled in the presence of peritonitis. This likely reflects the

increased severity of maternal illness and possible fetal compromise requiring urgent appendectomy and perhaps simultaneous delivery of the fetus [210]. One study of 94 pregnant patients with AA found that 12% of patients underwent CS as the mode of delivery, of which 7% were performed at the time of appendectomy [22].

The question could arise about the influence of conversion from LA to OA to the mother. Studies did not show increased rate of complications and increased maternal mortality. Caution should be present because of a small number of patients that had undergone such conversions [353]. Theoretically, if conversion is indicated, then mostly, (1) the anatomy is difficult, or (2) the inflammation is in an advanced stage in the form of perforation or abscess. Both situations result in longer operative time and a higher percentage of complications (see Sect. 1.10.4.7).

1.10.4 Fetal Outcome

1.10.4.1 General Considerations

The effects of any medical intervention on fetal mortality have to be considered in the context of certain preexisting background risks that are common to all pregnancies. These include a 3% risk of birth defects, 15% for miscarriage, 4% for prematurity, 4% for growth retardation, and 1% for mental retardation or neurological developmental problems. A variety of nonobstetric surgical interventions resulted in a spontaneous miscarriage (5.8%), premature delivery (8.2%), and major birth defect (2%) [354].

> Surgery (appendectomy) and general anesthesia are not significant risk factors for spontaneous abortion and do not increase the risk of major birth defects, even during the first trimester.

The use of dexamethasone for fetal lung maturity is relevant between 22 and 36 weeks of gestation, and facilities for caring of the preterm baby are obligatory [355].

1.10.4.2 Historical Perspective

In the nineteenth century, many pregnant patients with AA presented with consequences of advanced intraperitoneal inflammation. In that period miscarriage and preterm labor resulted in fetal mortality of 100% [95–97]. Fetal mortality was higher in years before 1990 at a time when the current possibilities offered by modern neonatology, fast and accurate (imaging) diagnostic workup, intensive care, and antibiotic therapy were limited or not available. Abrahams, in 1897, collected 15 cases from the literature and stated that the fetal mortality in cases of perforative AA during pregnancy, even when operated upon without delay, was as high as 90% [343]. In 1908, Babler reported more than 200 cases with a fetal mortality of 40%. Babler concluded that "the mortality of appendicitis complicating pregnancy is the mortality of delay" [339]. This statement was published several years earlier by Heaton [49]. Up to 1973, fetal mortality was 20% (perforated AA 30% and nonperforated AA 3%) and seems to be related to the severity of the disease rather than the period of gestation [249].

1.10.4.3 Fetal Mortality

When the appendix is not perforated (simple AA), fetal mortality is 0–5% [20, 22, 34, 38, 71, 85, 348], while perforation raises fetal mortality to 10–36% [22, 25, 26, 34, 71, 85, 348]. For a comparison, fetal mortality of 13.6% (1949–2005) is found when MD in pregnancy was the cause of acute abdomen [123].

Quite apart from the likelihood of premature labor, there exists a special risk of intrauterine fetal death if the infant is allowed to remain in utero in the presence of peritonitis. This may occur in any severe disease and is probably due to the continuation of high pyrexia together with bacterial toxemia (see Chap. 23). The prolonged rise in temperature must increase the metabolic rate and therefore the oxygen requirements of the fast-developing tissues. It is possible that a point is reached when the demand outstrips the supply, and this is at a time when the placental efficiency is diminishing. In addition, it is recognized that

fast-growing tissues are especially susceptible to noxious stimuli [356].

1.10.4.4 Fetal Morbidity

In the largest study with over 7100 patients, 16.9% of women delivered in the same admission [210]. Among the 1203 patients who delivered, there was a threefold increase in preterm birth. Unexplained antepartum hemorrhage was four times more likely to occur in patients with AA as well as placental abruption with a twofold increased risk among patients with AA. The accompanying systemic inflammation associated with AA and the close proximity of the appendix to the uterus may also lead to a neutrophil and inflammatory cytokine infiltration into the uterus (chorion and amnion) and lead to placental abruption or preterm birth [210]. Premature rupture of membranes and postpartum hemorrhage were less commonly seen in patients with AA, and the CS rate was comparable between groups [210]. Importantly, there was no increase in intrauterine death, and infants were less likely to be small for gestational age.

The risk of perforation increases with gestational age, and perforation in the third trimester often results in preterm labor [42]. Pushed away by the enlarging uterus, the omentum is not able to localize an appendiceal abscess, so that the uterus itself becomes the medial wall of the abscess. This irritant may precipitate premature labor. Peritonitis developed in 27% of pregnancies complicated by AA. There are no predictors among sociodemographic factors for peritonitis. Among delivering patients with AA, patients with associated peritonitis were more likely to deliver preterm and by CS [210]. In patients with uncomplicated AA rates of preterm delivery rate (7.7%) were within the range of total preterm delivery rate (10.9%), while the rate of preterm delivery when MD was the cause was 26% [123]. Compared to the general rate of preterm birth, which is 7.7–12.3%, appendectomy during pregnancy did not significantly increase preterm delivery [37, 357, 358]. Others claim significantly higher preterm delivery rate (10.9%) in patients with AA in comparison with normal pregnancy (4.4%) [203]. One of the hypotheses is that a lower intraoperative maternal systolic blood pressure is found during LA which could lead to a decrease in uterine blood flow, resulting in fetal stress, an elevated postoperative FHR, and eventual PTD [246]. These findings about fetal outcome can be summarized as [11, 20, 24, 25, 210, 211]:

- The increase in the preterm delivery:
  - During the first week after appendectomy (>23 weeks of gestation)
  - Age over 35
  - BMI greater than 30
  - Peritonitis
- Decrease in mean birth weight at term (<3000 g or even 2500 g)
- An increase of live-born infants dying within 7 days of birth
- No increase of stillborn infants
- No increase of congenitally malformed infants
- Negative appendectomy with positive uterine pathology/inflammation carries a significantly higher incidence of fetal loss and early delivery

In the largest study of 7114 patients and 1203 with the deliveries during the course of AA/appendectomy, infants of patients with AA were less likely to be growth restricted at the time of birth, which is in contrast to previous reports of the increased risk of fetal weights <3000 g [20] or even <2500 g [11]. This largest study only evaluated patients who delivered in the context of an AA, and there was no opportunity for placental insufficiency to develop or for the fetus to be exposed to the inflammatory environment and develop possible associated sequelae such as growth restriction over the remainder of the pregnancy. If authors had been able to follow patients who developed AA and delivered at a later time, the fetal weight at birth would be more helpful in determining the impact of AA on in utero growth. Furthermore, as only 1% of pregnancies with AA were complicated by growth restriction, this raises the possibility of a coding error and missing data as well.

1.10.4.5 Negative Appendectomy

The issue raised was the rate of increased fetal loss after appendectomy of a normal appendix. Fetal loss rate within 30 days and preterm delivery of 2–4% for both NA and non-perforated AA are reported [206, 211, 228, 251]. These percentages are even lower than in nonoperated pregnant population [359–361]. Therefore, it is questionable that NA causes adverse perinatal results [173, 251]. Some studies included complications in long-term follow-up after an appendectomy and did not take into account the expected number of perinatal and intrauterine deaths in the total (normal) pregnant population [41, 258]. Other studies have limitations because only fetal demise and early delivery occurring during the hospitalization in which the appendectomy was performed were reported.

Partly the same percentage in NAR and simple AA can be explained by other inflammatory causes (15% of cases) found during NA [206, 211]. Also, some studies did not exclude patients with previous history of (multiple) spontaneous abortions which are the confounding factors.

> The underlying (inflammatory) pathology not (the type of) the procedure has an influence on fetal risk rates. If no pathology is found during NA, there is no increase in fetal loss rate.

Others concluded that if there was an effect of surgical trauma on the fetoplacental-uterine elements, it should, in uncomplicated cases, have ceased approximately 1 week after appendectomy [20, 25]. In one study with negative laparotomy for suspected AA, those in whom no further surgery was performed were considerably more likely to continue their pregnancy undisturbed, compared to those who proceeded with appendectomy (89% versus 57%, respectively) [249]. This increased risk of delivery the week following surgery was present when performed after 23 weeks of gestation [24]. Any complication and increased risk of preterm delivery after that period in a patient without surgical complications should not be related to the operation itself [20, 25]. The premature delivery rate was often omitted in reports on AA, but it ranges 15–45% [19, 100, 362]. It is now believed that subclinical IAI is a cause of preterm premature rupture of membranes and/or preterm labor and, as such, is an important contributor to the leading cause of infant morbidity and mortality complications from prematurity (see Chap. 23).

There are several issues for discussion [206]. First, some authors included adverse perinatal outcomes even more than 30 days after the operation. Many of these patients had a history of previous multiple spontaneous abortions and should be excluded from this analysis. Second, when no other etiologies were identified during the exploration, it could be that the patients' abdominal pain was a sign of a pregnancy-related complication that was the underlying cause of the fetal demise. Third, in pregnant patients who underwent an NA, the percentage of LA was greater than in those with inflamed or perforated AA, and this difference may account for this observation. Fourth, NA was present most frequently during the first trimester. Generally, the incidence of miscarriage is the highest in the first trimester (10–15%) than the second (up to 5%) or third trimester (<1%) [363]. Fifth, more laparoscopic appendectomies are performed during the first trimester when there is a greater incidence of miscarriage.

1.10.4.6 Open vs. Laparoscopic Approach

OA and LA do not differ with respect to the incidence of preterm delivery, abortion, and CS [203, 241, 353], birth weight, gestational duration, rates of intrauterine growth restriction, congenital malformations, stillbirths, and neonatal deaths [364]. The association of spontaneous abortion with laparoscopy has been illuminated in several articles, which found that fetal loss was significantly higher in LA than OA (5.6–7% vs. 3.1%), despite a higher rate of non-appendicitis in the laparoscopy group [143, 228]. However, because one of these studies was conducted only on patients with complica-

tions that occurred during the hospital stay after an appendectomy, there was a selection bias, and its persuasive power is weak. Others did not find the difference between two approaches [203, 229] or did not have fetal loss with LA [229, 232, 233, 365, 366]. It is almost certain that the subsequent spontaneous abortions and fetal demise are associated with maternal disease severity rather than with operative technique.

1.10.4.7 Conversion from Laparoscopic to Open Approach

Studies did not show an increased rate of fetal mortality and preterm delivery. In the OA, the preterm delivery rate was 11.8% vs. 15.8% in the LA [353]. Caution should be present because of a small number of patients that had undergone such conversions [353]. Theoretically, if conversion is indicated, then mostly (1) the anatomy is difficult, or (2) the inflammation is in an advanced stage in the form of perforation or abscess. Both situations result in longer operative time, higher incidence of uterine manipulation, and a higher percentage of complications. Currently, studies show a low (1%) rate of conversion to laparotomy that is better than most published rates of nonpregnant patients [228]. It may reflect the fact that the LA in pregnancy is usually performed by experienced surgeons [228, 229].

1.10.4.8 Long-Term Outcome

In most reports, the length of follow-up is not defined, and the conclusions are, for LA, in the form of "The follow-ups of all the infants were uneventful" [227]. In a long-term follow-up, LA in pregnancy was shown to be safe and efficacious, without any long-term effects to the fetus or resulting child [352], without developmental delays in children up to 9 years old, regardless of the trimester in which the procedure was performed [367]. Children may demonstrate acquisition of developmental skills at varying rates. However, all children had a normal motor, sensory, and social development by 3 years of age. A larger study evaluating child development based on a normal range would draw more definitive conclusions.

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2 Acute Biliary Tract Disease

Abstract

The most common causes of the gallbladder disease in pregnancy are gallstones and biliary sludge. The incidence of gallbladder disease in pregnancy is 0.05–0.3%, and asymptomatic gallstones occur in 3.5–10% of all pregnancies. The incidence of acute cholecystitis during pregnancy is one of the highest of nonobstetric operative conditions, and 40% of pregnant patients with symptomatic cholelithiasis require cholecystectomy during pregnancy. Natural history and clinical examination are similar as in nonpregnant population. Detailed therapeutic modalities include medical, open surgical, and laparoscopic procedures. 1/1200 pregnancies are complicated by common bile duct stones. Common bile duct stones have been observed in 10–12.5% of pregnant women undergoing cholecystectomy and account for 7% of cases of jaundice in pregnancy. Diagnostic workup and therapeutic management are complex and depend on the status of the mother, severity of the disease, presence of infection, duration of pregnancy, and status of the fetus.

2.1 Acute Cholecystitis/Biliary Colic

2.1.1 Historical Perspective

A notable discovery in the last century by Von Recklinghausen that 90% of women having gallstones have been gravid at least once and the subsequent findings by Courvoisier in autopsy studies that three times as many women have gallstones as men hinted at the possibility of pregnancy being one of the major factors in the development of cholelithiasis [1].

2.1.2 Incidence

2.1.2.1 General Population

The prevalence of gallbladder disease in general population differs significantly in different populations and among countries. William Mayo made a statement that gallstones occur three times more frequent in women [2]. In the United States, 10–15% of the adult population has gallstones. In particular, 70% of Native American women older than 30 years develop cholelithiasis. Mexican

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_2

American women have an intermediate prevalence of about 14% with Caucasians and Black women at 4% and 5%, respectively [3]. Chilean women are also reported to be at high risk for developing gallstones [4], and populations of Latin American countries have the prevalence of gallstones up to 50% in adult women [5].

2.1.2.2 Pregnancy and Puerperium

In 1910, Peterson collected 25 cases of cholecystitis during pregnancy, 10 of these were during puerperium [6]. The ages of the patients were recorded in 21. The age distribution during pregnancy was 20–25 years, four cases; 25–30 years, eight cases; 30–35 years, six cases; and 35–40 years, three cases. The age distribution during the puerperium was 20–25 years, three cases; 25–30 years, one case; 30–35 years, one case; 35–40 years, one case; and over 40 years, one case.

The incidence of gallbladder disease in pregnancy is 0.05–0.3% [7–10], and asymptomatic gallstones occur in 2.5–10% during pregnancy and 12% in early puerperium, versus 1.3% of nonpregnant controls [4, 11–13]. Approximately 60–69% of pregnant women with gallstones are asymptomatic [4, 12]. The incidence of acute cholecystitis during pregnancy is 1/1000–1/10,000 pregnancies [14–18], and 40% of pregnant patients with symptomatic cholelithiasis require cholecystectomy during pregnancy [19–21]. Cholelithiasis is the cause of cholecystitis in over 90% of cases.

Despite its relatively uncommon occurrence during pregnancy, 81% of women with symptoms of gallbladder disease had their first attack within 1 year of pregnancy [22]. Higher incidence of gallbladder disease of 0.39% is found in Saudi Arabia. This is attributed to [1] high number of repeated pregnancies and [2] genetic predisposition because higher percentages (7.5%) of pregnant women harbor silent gallstones in comparison to 3.5% in the Western countries [23]. There is no statistically significant difference in the prevalence rates for gallstones between Mexican-born and non-Mexican-born pregnant Hispanic women in the 20-year to 49-year age group [24].

2.1.3 Risk Factors

Pregnancy may constitute a defined period of metabolic stress in which subclinical tendencies are transiently revealed. For example, pregnant women with gestational diabetes or high blood pressure are at risk of later developing diabetes mellitus or hypertension [25, 26]. A similar phenomenon may happen with gallbladder sludge and stones [27].

2.1.3.1 Biliary Sludge

Biliary sludge, or microlithiasis, is a mixture of granules of cholesterol and calcium bilirubinate crystals up to 2 mm in diameter within viscous bile. Larger clusters are defined as gallstones (by ultrasound). Although not all cases of sludge will necessarily evolve to become gallstones, sludge is believed to be the initial step in gallstone formation and is regarded as the earliest recognizable stage of lithogenesis [28]. The presence of sludge in the first trimester of pregnancy correlated with a higher risk of developing gallstones.

Biliary sludge, a potential precursor to gallstones, forms in 11–31% of women during pregnancy, and gallstones form in 2–6% [4, 29–31]. New sludge or stones were found in 30% and 2% of the women, respectively, at the end of their pregnancies. Postpartum sonography revealed the disappearance of the sludge in 61% of those women who had previously demonstrated sludge and the disappearance of stones in 28% of those who had had stones [31]. After delivery, the disappearance of gallstones correlated with a smaller stone diameter and increasing age [31]. Therefore, some patients who have symptomatic cholelithiasis during pregnancy may not have it after delivery [30]. These results should be taken with caution because the sensitivity of ultrasound for microscopic sludge is only 50–60% [27]. All detected gallstones were <10 mm [4, 29].

2.1.3.2 Multiparity

Multiparity is a risk factor due to hormonal changes that directly influence on gallstone formation [29, 32]. Pregnancy increases prevalence from 1.3% in nulliparous women to 12.2% in multiparous [33]. Approximately 5.1% of women

develop gallbladder disease after one pregnancy, 7.6% after two pregnancies, and 12.3% after 3 or more pregnancies [27, 34–36]. After accounting for the number of children, 12 months of breastfeeding reduces the risk of gallbladder disease in parous women by 7% [37]. As estrogen levels fall during lactation, it is possible that the protective effect of breastfeeding could be mediated through estrogen [38], although there are other hormonal changes that occur with lactation that may also have an effect. Early marriage and repeated pregnancies until menopause make the probability of gallstone disease occurring in pregnancy higher. A cross-sectional study found following incidence of gallstones: 21–30 years age group of 1.4% in patients having no pregnancy, 9.6% in patients having one pregnancy, 7.1% in patients having two pregnancies, 6.0% in patients having three pregnancies, and 3.3% in patients having four and more pregnancies; in the 31–40 years age group, 0.6% in patients having no pregnancy, 1.4% in patients having one pregnancy, 6.0% in patients having two pregnancies, 8.2% in patients having three pregnancies, and 12.6% in patients having four and more pregnancies; in the 41–50 years age group, 0.8% in patients having no pregnancy, 0.6% in patients having one pregnancy, 4.4% in patients having two pregnancies, 4.4% in patients having three pregnancies, and 12.9% in patients having four and more pregnancies; and in the 51–60 years age group, 0.6% in patients having one pregnancy, 1.1% in patients having two pregnancies, 2.5% in patients having three pregnancies, and 14.3% in patients having four and more pregnancies. The risk of developing gallstone disease increases in association with increased number of parity, particularly among the younger women [39]. Valdivieso et al. found that 12% of women immediately after delivery had gallstones compared to 1.3% nulliparous group [4]. This finding is explained by the increase in progesterone secretion which remains high during the second and third trimesters leading to smooth muscle relaxation and hence gallbladder dilatation and stasis [40]. The incidence of gallbladder disease in the asymptomatic category was higher in patients of higher age and parity [6, 41]. Young patients with a higher parity are more prone to gallbladder disease [13, 41].

On the contrary some claim there is no effect and even that prevalence is reduced by a factor of 40 in comparison to nulliparae [12, 42]. The authors of one large study claim that the female-specific factors of prior pregnancy and number of prior pregnancies did not show measurable influence on the prevalence of gallbladder stones [43]. They claim that multiparity could be misinterpreted as a risk factor because several pregnancies carry sometimes more than 10 years of life and age is known and confirmed risk factor.

2.1.3.3 Obesity and Diabetes Mellitus

The risk of forming gallbladder sludge or stones during pregnancy is significantly higher in obese women (BMI $\geq$30 kg/m^2) than in normal weight (BMI <25 kg/m^2) or overweight (BMI 25.0–29.9 kg/m^2) [7, 27]. Insulin resistance, which increases with BMI, is one possible mechanism linking obesity to gallstones [44–47]. Fasting serum insulin, which may be used as a surrogate measure for insulin resistance, is a risk factor for prevalent gallstones [46, 48–50]. Women who formed gallbladder sludge or stones were significantly more insulin resistant. Multiple autopsy studies have documented a statistically significant increase in the incidence of gallstones in diabetes mellitus [35, 48]. Epidemiological studies in Mexican Americans [44] and in Caucasian Americans [36] have shown diabetes mellitus to be a significant risk factor for gallstones. This association was strongest for women whose prepregnancy BMI was <30 kg/m^2 [51]. The independent risk factor for incident sludge or stones is prepregnancy BMI [27]. Also, leptin may mediate the association between obesity and gallbladder disease [27]. As the prevalence of overweight and obesity in young women increases [52], pregnancy-associated gallbladder disease may become an even greater problem.

2.1.3.4 Oral Contraceptives

The strong association of the oral contraceptives usage and gallbladder disease shows that all pregnant patients with a history of oral contraceptive use must be submitted to ultrasound

examination of the gallbladder [41]. Modern low-dose oral contraceptives may be safer than older formulas, but the safety of oral contraceptives should be evaluated by studying bile saturation and biliary function rather than waiting for gallbladder disease to develop [53].

2.1.3.5 Age

Age is a known risk factor for gallstone disease in general population. Higher gallbladder stone prevalence in older persons is confirmed in sonographic studies [54–56], autopsy studies [57], and studies based on clinical symptoms [58]. It is questionable if multiparity is a risk factor and contributed long period of three and more pregnancies to age as a risk factor and not multiparity itself (see Sect. 2.1.3.2).

2.1.3.6 Gallbladder Volume and Function

Some authors have suggested that gallstone and biliary sludge formation during pregnancy may be related to increased fasting gallbladder volume [59], while others have favored postprandial gallbladder volume [60, 61]. Increases in both fasting and postprandial gallbladder volume have been reported by Everson et al. They suggested that gallstone and biliary sludge formation during pregnancy could be attributed to gallbladder motility dysfunction [62, 63]. A direct relationship between gallbladder hypomotility and gallstone and biliary sludge formation during pregnancy in a group of healthy pregnant women has been shown [29].

2.1.4 Pathogenesis

2.1.4.1 Estrogens/Progesterone

Cholesterol gallstones are more common in women than men, and this gender difference begins since puberty and continues through the childbearing years [5, 64]. Pregnancy is associated with an increased percentage of colic acid, increased cholesterol secretion, increased bile acid pool size, decreased enterohepatic circulation, and a decreased percentage of chenodeoxycholic acid [65].

Progesterone

The progesterone-induced smooth muscle relaxation of the gallbladder reduces gallbladder emptying and promotes stasis of the bile [66, 67]. Progesterone also reduces bile acid secretion and increases the risk of cholelithiasis and subsequently of acute cholecystitis [68]. Ultrasound findings in pregnant women show a decrease in the gallbladder emptying rate and an increase in fasting and residual gallbladder volumes after emptying in the second and third trimesters. In addition, incomplete postprandial gallbladder emptying has been reported in pregnant women [60, 63, 69].

Estrogen

Estrogen increases the risk for the formation of cholesterol gallstones by promoting hepatic secretion of biliary cholesterol that induces an increase in cholesterol saturation of the bile [70–73]. In addition, high levels of estrogen significantly enhance the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis, even under high dietary cholesterol loads [73, 74]. These findings suggest that there could be an increased delivery of cholesterol to the bile from de novo synthesis in the liver. Furthermore, estrogen could augment the capacity of dietary cholesterol to induce cholesterol supersaturation of the bile [74, 75], and high doses of estrogen augment intestinal cholesterol absorption [75]. During estrogen treatment, cholesterol is synthesized even with its excess availability from the high cholesterol diet. Loss of negative feedback regulation of cholesterol biosynthesis results in excess secretion of newly synthesized cholesterol and supersaturation of the bile that predisposes to cholesterol precipitation and gallstone formation [73]. Therefore, the most common type of stones in pregnancy is yellow cholesterol stone(s) [5, 27]. Additionally, high levels of estrogen could impair gallbladder motility function and consequently induce gallbladder hypomotility [76]. Since plasma hormone concentrations increase linearly with duration of gestation, the highest risk of gallstone formation is in the third trimester of pregnancy.

In addition, estrogen could decrease plasma low-density lipoprotein (LDL) cholesterol and increase plasma high-density lipoprotein (HDL) cholesterol [77, 78]. The decrease in plasma LDL is a result of increased hepatic LDL receptor expression, which increases the clearance of plasma LDL. Therefore, the increased uptake of LDL by the liver may result in increased secretion of cholesterol into the bile. These alterations could induce an apparent increase in hepatic output of biliary cholesterol derived from circulating lipoproteins such as HDL and LDL, although LDL cholesterol could have a less effect on biliary secretion. Figure 2.1 illustrates the potential lithogenic

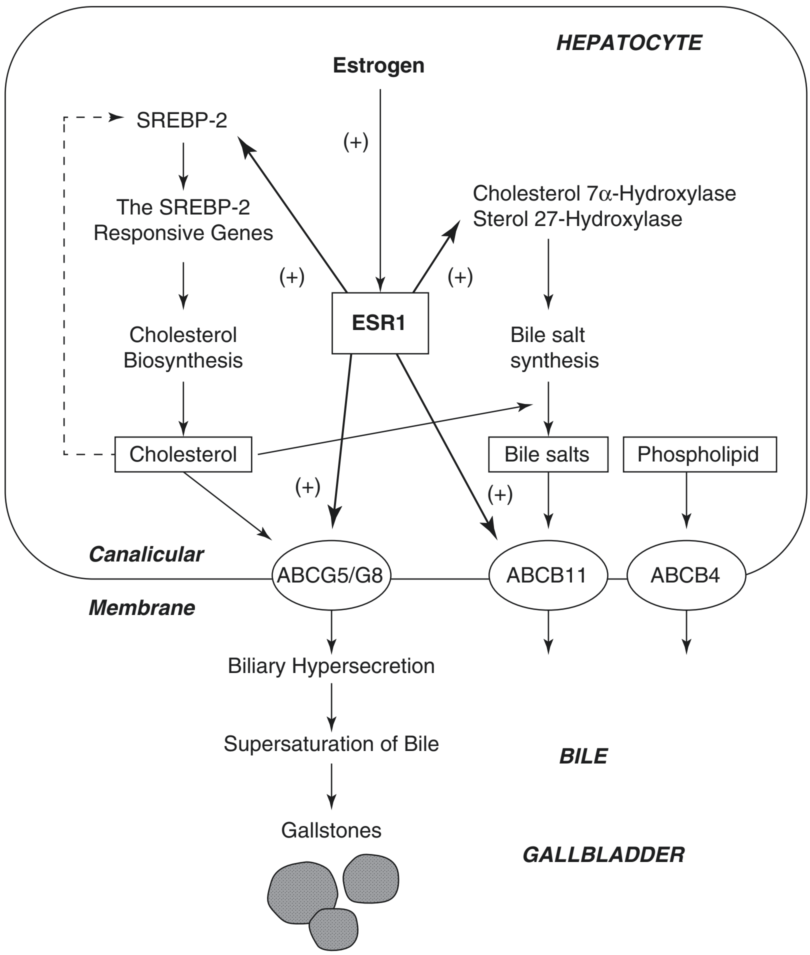

Fig. 2.1 The proposed model underlying the potential lithogenic mechanisms of estrogen through the estrogen receptor 1 (*ESR1*) pathway in the liver. In the liver, there is a possible "estrogen-ESR1-SREBP-2" pathway promoting cholesterol biosynthesis and hepatic secretion of biliary cholesterol. The negative feedback regulation of cholesterol biosynthesis (as shown in a *dashed line*) is inhibited by ESR1 that is activated by estrogen, mostly through stimulating the activity of sterol regulatory element-binding protein-2 (*SREBP-2*) with the resulting activation of the SREBP-2 responsive genes for the cholesterol biosynthetic pathway. Consequently, these alterations induce excess secretion of newly synthesized cholesterol and supersaturation of the bile that predisposes to cholesterol precipitation and gallstone formation. Moreover, the hepatic ESR1 activated by estrogen could stimulate the activity of ATP-binding cassette (*ABC*) transporters ABCG5 and ABCG8 on the canalicular membrane of the hepatocyte and promote biliary cholesterol secretion. Of special note is that these lithogenic effects of estrogen are inhibited by the antiestrogenic ICI 182,780. In addition, the estrogen effects on increasing cholesterol biosynthesis and promoting cholesterol gallstone formation are, in part, blocked by deletion of the *ESR1* gene. Reproduced with permission from [85]

mechanisms of estrogen through the ESR1 pathway in the liver. There is a high rate of gallstone/sludge dissolution in the first month after delivery [79, 80]. The rate of disappearance of gallstones and biliary sludge is 15–28% and 39–68%, respectively [31, 81]. Spontaneous disappearance of gallstones after delivery is significantly more frequent in older women [31]. Speculation is that small gallstones are ejected from the gallbladder during the postpartum period when gallbladder contraction restores, as early as 2 weeks after delivery [61], and some of these women develop acute pancreatitis (AP). In contrast, in older women with reduced gallbladder contractility, most gallstones likely remain in the gallbladder until dissolved by less lithogenic bile. Thus, AP associated with pregnancy usually occurs in young postpartum women and is usually due to gallstones [31].

The use of oral contraceptive steroids and conjugated estrogens in premenopausal women doubles the incidence of cholesterol gallstones [82–84]. In addition, the administration of estrogen to postmenopausal women and estrogen therapy to men with prostatic carcinoma displays similar lithogenic effects [70–72]. These observations support the concept that higher risks for cholesterol gallstones in women than in men are related to differences in how the liver handles cholesterol in response to estrogen [84].

2.1.4.2 Insulin

Apart from hormone, insulin resistance is also responsible for gallstone formation. The exact mechanisms are not clear. Cholesterol is the primary constituent of gallstones formed during pregnancy. Cholesterol gallstone formation requires several pathogenic factors, including supersaturation of hepatic bile with cholesterol and altered gallbladder motility. Hyperinsulinemia and insulin resistance may affect either of these factors. Hyperinsulinemia increases cholesterol synthesis via the activity of the HMG-CoA reductase [86] and increases hepatic uptake of LDL cholesterol [87]. Insulin resistance is also associated with lower serum levels of HDL cholesterol, a known risk factor for gallstones [88]. Administration of insulin in diabetics increases biliary cholesterol saturation [89].

Data show greater degrees of biliary cholesterol saturation in patients with type II diabetes compared with controls [90, 91]. Insulin inhibits basal and cholecystokinin-stimulated gallbladder motility, and gallbladder dysmotility has been documented in patients with type II diabetes [92, 93]. In animal models, nonobese, diabetic mice have diminished gallbladder contractility and rapid formation of cholesterol crystals [94], while gallbladder contractility correlates inversely with glucose and insulin levels in obese animals [95]. Insulin resistance is associated with gallbladder dysmotility in nonobese, nondiabetic humans [96]. Therefore, insulin resistance, even in the absence of obesity, may lead to gallbladder sludge and stone formation, either by causing gallbladder dysmotility or by altering biliary lipid secretion. Insulin resistance may be a surrogate for other, undefined pathophysiologic mechanisms that lead to gallstone formation rather than a direct underlying cause [51].

Diabetics have an increased cholesterol saturation index in the bile compared with nondiabetics [97]. In addition, gallbladder fasting volumes are larger, and gallbladder motility is diminished in non-insulin-dependent diabetics compared with nondiabetics [98, 99]. Hyperinsulinemia is characteristic with non-insulin-dependent diabetes as a result of insulin resistance, and there is an association between hyperinsulinemia and an increased prevalence of gallbladder disease [44, 46, 47]. Both hyperglycemia and euglycemic hyperinsulinemia inhibit CCK-stimulated gallbladder motility [92]. Hyperinsulinemia may also be a key factor because insulin regulates the Na^+-K^+ pump, which may adversely affect the ionic and osmotic homeostasis of smooth muscle cells including gallbladder myocytes [100]. The Na^+-K^+ pump of presynaptic nerve terminals is also regulated by insulin [100]. Moreover, decreased Na^+-K^+ pump activity can result in increased intracellular Na^+, which in turn increases the Na^+-Ca^{2+} exchange, thereby increasing intracellular calcium. Increased intracellular calcium will alter both smooth muscle tone and release of neurotransmitters. Moreover, the gallbladder myocytes from obese, diabetic mice are foreshortened and respond poorly to cholecystokinin (CCK) [101].

Insulin resistance and/or diabetes may also affect alterations in the density or sensitivity of acetylcholine or CCK receptors or prevent neurotransmitters from accessing their receptors. Sugars can react nonenzymatically with amino groups in proteins, lipids, and nucleic acids to form advanced glycation end products [102]. These products cause covalent cross-linking of collagen and protein matrix [102]. The cross-linking of the matrix may lead to stiffening of the gallbladder wall itself, limiting its contraction, or may impair CCK egress through blood vessel basement membranes, preventing CCK interaction with neural or myocyte receptors.

2.1.4.3 Obesity

One potential explanation for the differences in gallbladder dynamics observed between obese and lean individuals may be due to the differences in serum and, perhaps, gallbladder wall lipids [103]. As a result, the smooth muscle cell cholesterol/phospholipid ratio increases and membrane fluidity decreases [103]. Therefore, these obese subjects with high serum total and LDL cholesterols as well as triglycerides may also have high gallbladder lipids, which may play a role in gallbladder function.

2.1.4.4 Other

There is also a 50% increase in the bile acid pool associated with a concomitant steroid-induced increase in cholesterol secretion during pregnancy. Together with the replacement of deoxycholic and chenodeoxycholic bile acids with cholic acid, increased volume and decreased motility of the gallbladder enhance the development of biliary stones [22].

2.1.5 Clinical Presentation

2.1.5.1 Medical History

As early as 1911, William Mayo stated that quiescent gallstones often become active during pregnancy [2]. Symptoms of gallstone disease during pregnancy are the same as in nonpregnant patients [4, 104]. An episode of biliary pain usually begins with right upper quadrant or mid-epigastric pain which may increase in severity. Biliary colic begins quite suddenly and may radiate to the interscapular area, to the angle of the right scapula, or to the right shoulder. It may be precipitated by a fatty meal or by consumption of a large meal following a period of fasting. Typically though, biliary colic occurs in a diurnal pattern with pain peaking around midnight. Nausea and vomiting accompany episodes of colic in 50% of patients. Finally, 70–80% of patients will have a history of known gallbladder stones, colic attacks, and fatty food intolerance [14]. Increasing severity of colicky pain, fever, or chills (rigors) usually implies an underlying complication, i.e., cholecystitis, AP, or cholangitis. If persistent jaundice is present, common bile duct (CBD) stones should be suspected.

2.1.5.2 Physical Examination

During physical examination there are several signs that could be elicited:

- *Direct abdominal tenderness* in the upper right quadrant. Due to somewhat distant locations of the enlarging uterus and gallbladder, there is no significant blunting of symptoms and signs.
- *Murphy's sign* (cessation of inspiration during palpation of the inflamed gallbladder) may be elicited less frequently in pregnant patients and indicates acute cholecystitis [105].
- *Abdominal muscle rigidity* is present only with gallbladder perforation and biliary peritonitis, but abdominal wall laxity in late pregnancy might mask the classical signs of peritonitis [106].
- *Fever* and *tachycardia* are variably present and not sensitive signs. The more advanced the disease, the more pronounced these symptoms and signs are.
- *Vomiting, dyspepsia,* and *itching* are not associated with asymptomatic biliary sludge or stones. Biliary pain is associated only with the presence of stones, and it is important that only women with "old" stones experienced biliary pain [31].

2.1.6 Differential Diagnosis

There are many diseases that present with the pain in the upper right abdominal quadrant. But with adequate history taking and clinical examination, most of them could be excluded. The list of the most common differential diagnoses is presented in Table 2.1.

2.1.6.1 Hyperemesis Gravidarum

Hyperemesis gravidarum can be defined as intractable nausea and persistent vomiting associated with weight loss greater than 5% of pre-pregnancy body weight and ketonuria [107]. It occurs in 0.5–1.5% of pregnancies [107] and is more common in nulliparous in contrast to multiparous women that are prone to cholelithiasis and cholecystitis [108]. Hyperemesis gravidarum leads to dehydration, and hospitalization is usually required for intravenous fluid therapy [108]. This disorder presents early in the first trimester of pregnancy. As a rule, symptoms resolve before the second part of pregnancy, regardless of therapy. Jaundice is uncommon and, if present, is not associated with abdominal pain or fever.

Table 2.1 Differential diagnosis of right upper quadrant pain in pregnancy

Jaundice[a]	No jaundice
CBD stones	Diaphragmatic myocardial infarction
Hepatitis	Acute appendicitis
Intrahepatic cholestasis	Pancreatitis
Preeclampsia-eclampsia	Symptomatic/perforated peptic ulcer
HELLP syndrome	Pyelonephritis/nephrolithiasis
Acute fatty liver in pregnancy	Radiculopathy
Hepatic malignancy	Herpes zoster (Shingles)
Cholangitis	Perihepatitis (Fitz-Hugh-Curtis sy.)
Hepatic vascular engorgement	Rib fracture/Costal margin pain
Hepatic hematoma	Pleural effusion
	Pneumonia
	Colon cancer (hepatic flexure)

[a]Jaundice in these conditions is not obligatory

Abnormal liver tests are common, but the exact frequency is unknown. A frequency of 16% has been found [109]. The most striking abnormality is the elevation of aminotransferases with ALT levels exceeding AST levels as it is usual in nonalcoholic and noncirrhotic liver diseases [109]. ALT levels are variable, and hepatitis serologies are useful in the differential diagnosis especially when ALT levels are above ten times the upper normal limit or when it is the first affected pregnancy. The associated drug-liver injury should be systematically searched, especially when jaundice is present. Liver biopsy is not needed. Pregnancies complicated by hyperemesis gravidarum have been associated with transient hyperthyroidism, which usually requires no specific therapy [108].

2.1.6.2 Perihepatitis (Fitz-Hugh-Curtis Syndrome)

Perihepatitis (Fitz-Hugh-Curtis syndrome) is the result of early bacteremic or retroperitoneal lymphatic dissemination of *Chlamydia trachomatis* or gonococcal pelvic infection [110]. The syndrome is most frequently seen in young women and is more common in the second and third trimesters and puerperium. Inflammation in the right upper quadrant produces perihepatic adhesions. Classically, there is sudden onset of sharp right upper quadrant pain, often pleuritic in quality. Nausea and hiccups are occasionally noted. Physical findings include tenderness under the right costal margin, occasional hepatic friction rub, and fever. Pelvic examination may be normal or may reveal signs of cervicitis or pelvic inflammatory disease. Liver function tests and cholecystogram may be transiently abnormal. The diagnosis is suggested by a history of recent pelvic infection, but the syndrome can be a sequela of latent or asymptomatic infection. The diagnosis is further supported by isolation of gonococcus on cervical culture and improvement on appropriate antibiotics [110]. It is important to exclude other etiologies because there is no specific diagnostic marker of this syndrome.

2.1.6.3 Costal Margin Pain

In 1921, Alexander Tietze first described a syndrome characterized by a painful affliction of the costochondral cartilages (the area between the ribs and costal cartilages) [111]. The cause of the pain is recurrent, repetitive irritation of the intercostal nerves, not a synovitis of the interchondral cartilages. These factors support the hypothesis that direct or indirect trauma is the cause of the syndrome. Costal margin pain and tenderness due to stretching of muscular attachments are not uncommon during pregnancy. Upon physical examination, the pain is clinically recreated when the rib margins are displaced upward and anteriorly; thus, the *hooking maneuver* can be used to corroborate the diagnosis (Fig. 2.2). *Carnett's sign* can be used for confirmation. The patient is asked to lift the head and shoulders from the examination table to tense the abdominal muscles. An alternative is to ask the patient to raise both legs with straight knees. A painful, positive test increases the likelihood that the abdominal wall and not the abdominal cavity is the source of the pain. If a conduction block is used for diagnostic purposes only, then another block may be performed using long-lasting local anesthesia with 0.5% bupivacaine. After delivery (and ideally breastfeeding), a combination of local anesthesia 0.5% bupivacaine and 40 mg triamcinolone (FDA category C) can be used. This has been found to relieve the problem unless further trauma recreates the pathology. If residual pain persists or reoccurs, then repeated local anesthesia steroid blockade may be performed.

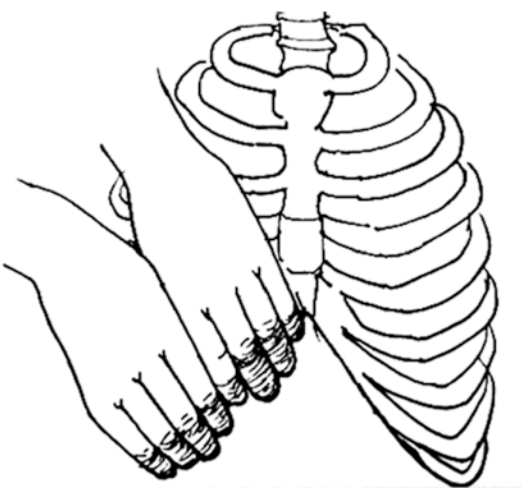

Fig. 2.2 Schematic illustration of the *hooking manoeuvre*. The fingers are hooked beneath the costal margins, displacing them upward and anteriorly. Reproduced with permission from [112]

2.1.7 Diagnosis

2.1.7.1 Laboratory Findings

If there is clinical suspicion of acute biliary colic or cholecystitis, the patient should be sent to the hospital for further evaluation. The difficulty in establishing the diagnosis is physiological leukocytosis up to 20,000/ml at labor in normal pregnancy and is not diagnostic. Only granulocytosis (left shift) indicates a bacterial infection. C-reactive protein (CRP) is elevated and significant, and bacterial infection is expected if values over 40 are found. The erythrocyte sedimentation rate (ESR) is physiologically elevated and thus is a less reliable monitor of inflammatory activity during pregnancy [113]. Serum bilirubin and transaminases may be elevated, as in nonpregnant women. Serum alkaline phosphatase is less helpful because estrogen causes its elevation (levels may double during normal pregnancy). Serum amylase levels are elevated transiently in up to 33%. Finally, postprandial plasma levels of total bile acids progressively increase during pregnancy.

2.1.7.2 Transabdominal Ultrasound

Adequate visualization of the gallbladder in pregnancy is 95–98% [41, 114, 115]. The remaining patients, whose gallbladder could not be visualized initially, are diagnosed as having chronic cholecystitis with contracted gallbladder and thickened gallbladder wall on the rescan [41]. Gallbladder sludge (see Sect. 2.1.3.1) is sonographically visible as the accumulation of the bile and is reported in as many as 30% of gravid patients with a similar proportion of women affected by the postpartum

period [27]. Sonography in early pregnancy confirms the physiological expansion of the gallbladder and the accumulation of stones, debris, and bile. Ultrasound findings of the gallbladder in healthy pregnant women show a decrease in the emptying rate and an increase in residual volume after emptying. If gallstones are the only pathologic finding, then the state is defined as biliary colic. For the diagnosis of acute cholecystitis, further findings should be present:

- Gallbladder calculi
- Wall thickening (>3 mm)
- Pericholecystic fluid
- Sonographic Murphy's sign (focal tenderness under the ultrasound transducer positioned over the gallbladder)

Another finding that should be ruled out is CBD obstruction because confirmation or suspicion changes therapeutic approach. It is suspected or confirmed if these findings are present:

- CBD >7 mm in diameter
- Dilatation of intra- and extrahepatic ducts
- Gallbladder calculi smaller than cystic duct diameter

A patient with abdominal pain from a suspected urinary tract calculus is better evaluated with ultrasound. Although the diagnosis of calculus is complicated by the presence of pregnancy-related hydronephrosis, the addition of color Doppler imaging of the bladder to identify ureteral jets and transvaginal ultrasound to detect stones in the distal third of the ureter help in the evaluation [116].

2.1.7.3 Endoscopic Ultrasound

See Sect 2.2.5.5.

2.1.7.4 Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) may be particularly helpful in differentiating CBD stones (see Sect. 2.1.7.4) from intrahepatic cholestasis of pregnancy because the clinical and biochemical presentation of these two entities overlaps [117]. MRCP is indicated if dilatation of intrahepatic and extrahepatic ducts (Fig. 2.3) is present on abdominal ultrasound (see Sect. 2.2). It can also differentiate between CBD stones and external compression due to Mirizzi syndrome (Fig. 2.4).

Additionally, because the pancreas is frequently obscured by overlying bowel gas during ultrasound evaluation, MRCP can often better evaluate the pancreas for edema, the pancreatic duct for obstruction in the setting of biliary AP, and the peripancreatic tissues for inflammation. The European Society of Urogenital Radiology (ESUR) established its Contrast Media Safety Committee in 1994. Table 2.2 presents the ESUR guidelines from 2006 for the use of

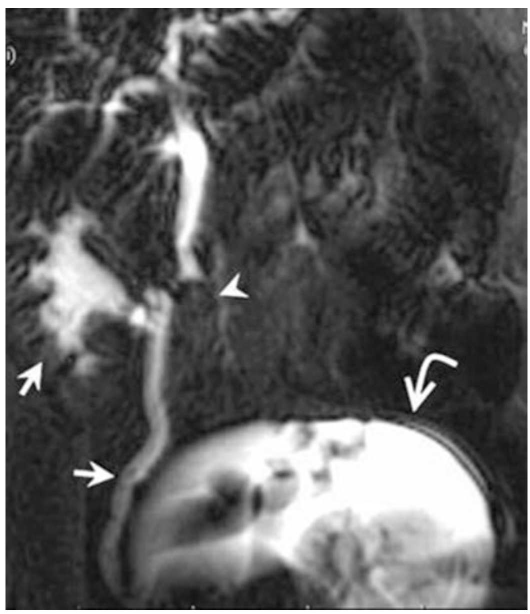

Fig. 2.3 CBD stones in the second trimester of pregnancy. Magnetic resonance cholangiopancreatography (MRCP) shows distal CBD obstruction due to a calculus (*arrowhead*), gravid uterus (*curved arrow*), and physiological right hydronephrosis and hydroureter (*arrows*). Reproduced with permission from [118]

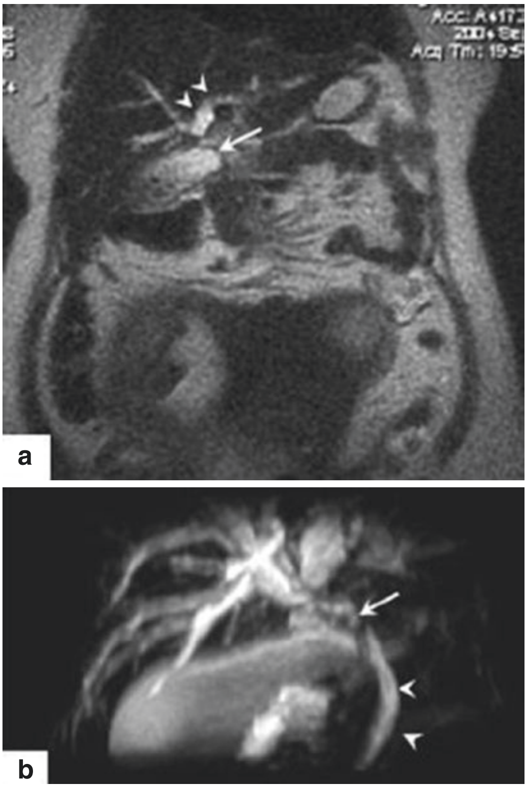

Fig. 2.4 A 27-year-old female at 36 weeks gestation with obstructive jaundice and right upper quadrant pain. (**a**) Coronal T2-weighted single-shot fast spin-echo image shows distended gallbladder with cholelithiasis (*arrow*) and intrahepatic biliary dilatation (*arrowheads*). (**b**) Thin-slice MR cholangiopancreatography (MRCP) images showed that the distal common bile duct is normal in caliber, and the common hepatic duct was compressed by the inflamed and distended gallbladder. Reconstruction of thin-slice MRCP images demonstrates the distended gallbladder fundus compressing the proximal common bile duct (*arrow*), causing intrahepatic biliary dilatation, and a normal caliber distal common bile duct (*arrowheads*), consistent with Mirizzi syndrome. Reproduced with permission from [119]

iodinated and gadolinium contrast media during pregnancy [120].

It should be noted that using modern diagnostic modalities for correct diagnosis of biliary origin of the acute abdomen during pregnancy is very high. It can be presented as an *index of wrong diagnosis*:

Index of wrong diagnosis (%) = provisionally diagnosed cases – confirmed cases × 100 provisionally diagnosed cases

Table 2.2 ESUR guidelines for the use of iodinated and gadolinium contrast media during pregnancy and lactation

	Iodinated agents	Gadolinium agents
Pregnancy	(a) In exceptional circumstances, when radiographic examination is essential, agents may be given to the pregnant female (b) Following administration to the mother, thyroid function should be checked in the neonate during the first week	(a) When MR examination is necessary, agents may be given to the pregnant female (b) Following administration of agents to the mother, no neonatal tests are necessary
Lactation	Breast feeding may be continued normally when agents are given to the mother	Breast feeding may be continued normally when agents are given to the mother
Pregnant or lactating mother with renal impairment	No additional precautions are necessary for the fetus or neonate. Follow ESUR guidelines for contrast media administration when renal function is impaired	No additional precautions are necessary for the fetus or neonate. Follow ESUR guidelines for contrast media administration when renal function is impaired

For acute appendicitis in pregnancy, it is around 40% and only 8.5% for acute cholecystitis in pregnancy [121].

2.1.8 Treatment

2.1.8.1 Historical Perspective

In 1890 Robert Barnwell Rhett, Jr. (Fig. 2.5), wrote of a cholecystotomy on a pregnant woman. In 1893, Boorse mentioned a case of pregnancy complicated by the expression of biliary calculi. In 1893, Willien reported a cholecystotomy in the third month of pregnancy. In 1895, Vineberg reported two cases of cholecystitis in the puerperium and said that he was able to find but four cases previous to his article. In 1895, Davis AB reported a case of cholecystectomy in the seventh

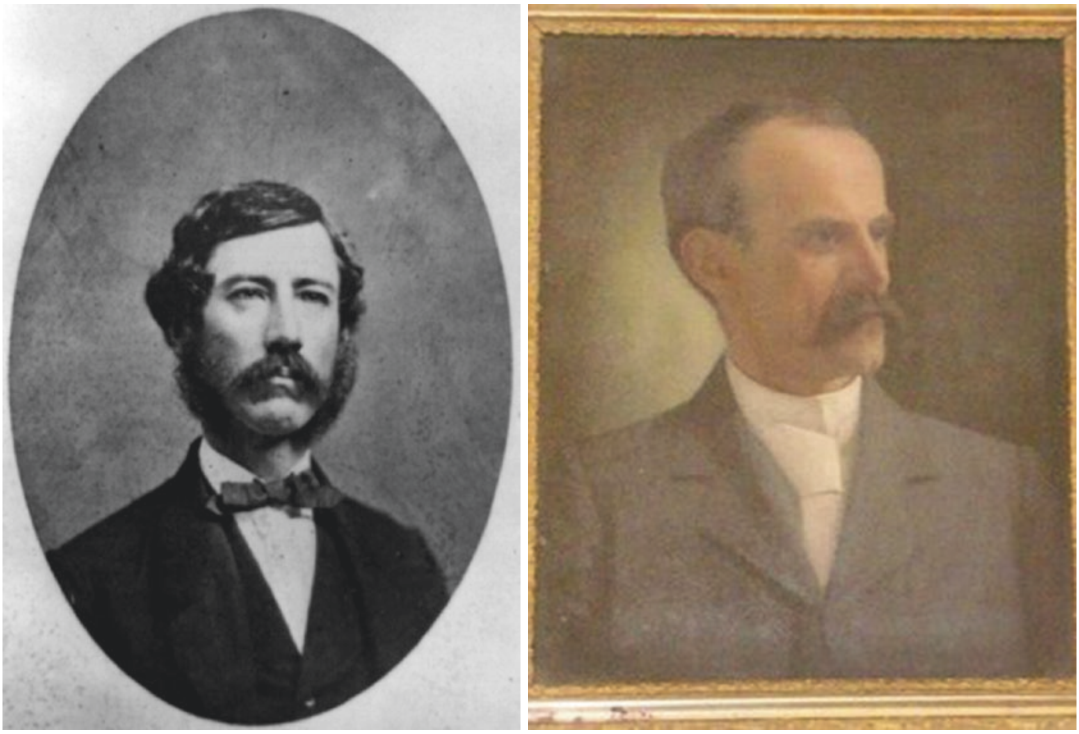

Fig. 2.5 Robert Barnwell Rhett Jr. (Huntsville, 1853–Charleston, 1901), President of the Medical Society of South Carolina and Dean of the Charleston Medical School, performed the first cholecystotomy on a pregnant patient in 1890. Reproduced with permission from [129]

month without interrupting the pregnancy. Ploger in 1910 gave a record of 42 cases, of these 22 had gallstone colic in the puerperium, and in 19 of these, it was the first attack. The remaining 20 attributed the beginning or increase in the severity of their gallstone pains to some pregnancy [122]. Peterson collected 25 cases complicating pregnancy including his own case and 10 complicating the puerperium. These are cases proved by operation or through the finding of calculi in the stool [6]. Otherwise, he could have included 20 cases of Huchard and 51 of Berline-Herwig. Since 1910, Green reported two cases following a miscarriage [123]; Branson, four cases [124]; Audebert, one case; and Graham, six cases, a rather meager list when the frequency of gallstone operation is considered [125]. Schroeder says that 90% of women operated upon have borne children. Peterson found that 75% had children. Grube proves that of 657 cases of gallstone, 613 cases had children. There were 183 married and 33 unmarried or sterile women [126]. Grube concisely states that pregnancy produces changes in the biliary system: (1) stasis of the bile, (2) increase of cholesterin in the bile, (3) protein decomposition, (4) cell desquamation, and (5) hyperemia of the mucosa of the bile ducts [126]. He agrees with Hofbauer that cholelithiasis is due to the above processes plus bacterial infection and says that as a result of investigations of the liver of women who have died during or just before or after labor, all of the abovenamed conditions are characteristic of pregnancy [127]. M'Nee says that on the basis of the investigation carried on by himself and Ashoff, some forms of stones originate in the aseptic and uninflamed bladder. M'Nee believed there is a definite relationship between gallstones and pregnancy taking into consideration that the most common age of onset corresponds to the period of childbearing and the number of cases of gallstones in women who have borne children [128]. He believed that the pressure of the uterus causes stasis. He also found that the *cholesterme* contents

of the bile were greatly increased in five women who died during, just before, or after labor. These findings coincide with those of Grube. Peterson says that in pregnancy, it is significant that in nearly one-third of the cases, the period of onset is at that time of gestation when the uterus is approaching the level of the umbilicus, sending the intestines upward, and when the growing fetus is beginning to hamper the eliminative powers of the liver. In the puerperium in one-half of the cases, the attacks occurred during the first 7 days postpartum suggesting traumatism of the biliary passages during labor. He quotes Vineberg who says the great eliminative processes going on at this period, the change in the intra-abdominal pressure, and the forced rest in bed with attendant constipation all favor these attacks.

IUoway in 1889 reported a case of icterus gravidarum. The occurrence of jaundice is most important as its presence affects the uterine contents, and the nearer to term, the greater the possibility of exciting labor. Peterson found that in 15 of his 25 patients, jaundice was present. He seems to prove that pregnancy can produce jaundice in a constitutional way without the aid of obstruction in the shape of calculi. The operative mortality was 13%, for 23 cases [6]. This is influenced by the complications of CBD involvement and the degree and extent of inflammatory processes. The condition of pregnancy seems to have but little effect. The deaths reported were from rupture of the gallbladder, cases of empyema, or extensive or prolonged operative procedures required by the conditions found. The occurrence of miscarriage is dependent upon the pathology present more than upon the effect of the operation. In Peterson's cases, two started before operation and three after. All of the latter were cases of extreme infection with chills, fever, and jaundice. Graham reports a case in the sixth month in which the gallbladder was ruptured by a blow on the abdomen. At operation, three gallstones were found in the abdomen, one in the gallbladder and two in the cystic duct. He gives detailed histories of four others, which were operated upon during pregnancy, all of whom went to term. One other case refused the operation and died 2 years later from complete CBD obstruction. Luiz in discussing Graham's paper describes a case with gallbladder rupture during labor. The patient died of general peritonitis, and postmortem, 250 gallstones were found scattered through the abdominal cavity.

2.1.8.2 Conservative Treatment

Gallbladder disease is the most common nonobstetric cause of maternal hospitalization in the first-year postpartum [130]. Interests of both the mother and the fetus must be considered in therapy during pregnancy. Usually, these interests do not conflict, because what is good for the mother is generally good for the fetus.

There is the principal difference in treatment of biliary colic and acute cholecystitis. Traditionally, medical treatment is a method of choice for biliary colic (in general population). The therapy could be initiated or continued by primary care physician but only after the consultation with the gastroenterologist or abdominal surgeon. This recommendation is due to the fact that even after biliary colic, there is increase in the incidence of premature contractions [131] and even several fetal deaths occurred [132]. Initially, the patients should be seen every day for the first several days and then once a week. The patients with significant comorbidities should be hospitalized even for medical therapy. Another traditional indication for medical therapy is to delay the cholecystectomy until the second trimester when spontaneous abortion rate after open cholecystectomy is the lowest (12% in the first trimester and 5.6% in the second trimester) [133]. On the other hand, delay of surgery until the second trimester may lead to further complications of gallstone disease such as acute cholecystitis and biliary AP, risk of maternal malnutrition, and reduction in fetal growth rate caused by lack of maternal oral intake leading to higher spontaneous abortion rates and preterm labor (PTL) [104, 134–136]. In addition, the rates of PTL and preterm delivery (PTD) are 0% during the second trimester compared to 40% in the third trimester [133].

Current evidence favors surgical treatment of symptomatic biliary disease. Cesarean section (CS) rate in conservatively treated patients is significantly higher (35%) than in the patients who received cholecystectomy [131, 137].

Total Parenteral Nutrition

Total parenteral nutrition has been used as an effective alternative to surgical treatment of chronic cholecystitis in the second and third trimesters [138], with no adverse effect on maternal weight gain and fetal growth [139]. The growing fetus requires essential fatty acids and amino acids for development and maturity of vital organs like the brain and lungs. Parenteral nutrition provides a viable means for the fetus to receive these supplements. A recent trend is to use peripherally inserted central catheters (PICC) because of a lower rate of major complications and relative ease of insertion compared to central venous catheters. PICCs should always be considered particularly in high-risk populations like pregnant women, taking into account a higher rate of minor complications like thrombophlebitis [140, 141]. PICC insertion is highly operator dependent, and lowest complication rates have been reported in the most experienced centers.

Diet

A low-fat diet is essential, minimizing intake of cholesterol-rich foods like foods of animal origin, pork and red meat, with slow reduction of body weight and by indulging in more fruits and fiber intake. Potent natural remedies minimize the abnormal concentration of bile acids (acids that help in fat digestion), keep cholesterol level in check, heal inflammation, clear out toxins, and eliminate the excess of lipids from the body. Beetroot juice is high in fiber and has carotenoids and flavonoids that reduce the cholesterol from entering the gallbladder and thus stops the formation of solid pear-shaped gallstones. It has betaine that supports liver function and tames high sugar level. Apple juice has a unique compound – malic acid – that helps in softening the gallstones and disintegrates. A mix of raw juice comprises carrot juice, cucumber juice, and beetroot juice. The maximum concentration should be of carrot juice. Cucumber juice has silica that prevents overformation of calcium stones in the body.

Pain Management

See Chap. 21.

Anticholinergic Antispasmodics

Dicyclomine (FDA category B) passes into breast milk and could affect a nursing infant. Dicyclomine can suppress the production of breast milk in nursing mothers.

Antibiotics

See Chap. 21.

Ursodeoxycholic Acid

Ursodeoxycholic acid, a naturally occurring bile acid agent, can dissolve gallstones by changing the composition of the bile, and it has been used in nonpregnant patients. Although ursodeoxycholic acid has been administered in pregnancy in the management of intrahepatic cholestasis, its safety and efficacy for the treatment of gallstones during pregnancy have not been established [142].

2.1.8.3 Percutaneous Biliary Drainage

Pregnant patients presenting with recurrent gallbladder colic during the first or third trimester or high-risk patients could be managed with percutaneous transhepatic gallbladder aspiration (drainage). Under ultrasound guidance and local anesthesia, a pigtail drainage tube is inserted through the liver and into the distended gallbladder. Essentially, it is recommended that the drainage tube should not be extracted until a fistula forms around the tube (≈2 weeks) in severe cases where changing of the drainage tube is necessary. Major disadvantages of this procedure are bile leakage, bile duct injury, and abdominal abscess. Although the patients both delivered without neonatal complications and subsequently underwent LC postpartum, not enough data are available for recommending this approach routinely [143].

2.1.8.4 Operative Treatment

Recommendations for General Population

The early operation of acute cholecystitis is recommended in general population [144]. Comparison of early open cholecystectomy (OC) with delayed OC found that early surgery had the advantages of less blood loss, a shorter operation time, a lower complication rate, and a briefer hospital stay [40]. Further, laparoscopic cholecystectomy (LC)

performed during the first admission was associated with a shorter hospital stay, quicker recovery, and reduction in overall cost of treatment compared to OC [145, 146]. Early LC is now accepted to be sufficiently safe for routine use because earlier reports of increased risk of bile duct injury have not been substantiated by more recent experience [145, 146].

According to the updated Tokyo guidelines [144], acute cholecystitis has three grades related to the severity of the disease:

- *Mild* (*grade I*): Early LC is the preferred procedure.
- *Moderate* (*grade II*): Early cholecystectomy is performed. However, if patients have severe local inflammation, early gallbladder drainage (percutaneous or surgical) is indicated. Because early cholecystectomy may be difficult, medical treatment and delayed cholecystectomy are necessary.
- *Severe* (*grade III*): Urgent management of organ dysfunction and management of severe local inflammation by gallbladder drainage and/or cholecystectomy should be carried out. Delayed elective cholecystectomy should be performed later when cholecystectomy is indicated.

Indications in Pregnant Population

Complications of gallstones represent the second most common non-gynecologic condition requiring surgery in pregnancy with cholecystectomy performed in 1–8/10,000 pregnancies [147]. At least 0.8% of women with gallbladder disease underwent cholecystectomy in the first postpartum year [27]. Because more than 4 million women give birth annually in the Unites States [148], estimation is that more than 32,000 young, otherwise healthy women will require postpartum cholecystectomy each year. Thus, pregnancy-associated gallbladder disease is a significant problem in young, otherwise healthy women.

The most common indication for biliary surgery during pregnancy is repeated biliary colic (37–70% of cases), followed by acute cholecystitis (20–40%), CBD stones (7%), and biliary AP in the remaining 3% [20, 135, 149]. Conservative medical management of symptomatic cholelithiasis in pregnant women often leads to suboptimal clinical outcomes. The maternal illness may pose a greater threat to the fetus than surgery.

The readmission rate for pregnant patients with biliary tract disease has been greater than 50% in patients managed conservatively, and 16% had either spontaneous abortions or PTDs [104, 132]. Recurrence rate during pregnancy is 31–38% for symptomatic cholelithiasis, and patients in the second trimester had the highest rate of relapse, followed by the first and then the third trimester [131, 150]. There are reports with even higher recurrence rates (40–92%) after conservative treatment confirming its trimester dependency [10, 132, 134, 151]. Studies report an average of 2–6 relapses during pregnancy [10, 131, 132, 152], each lasting 5–8 days [131]. Also, the disease is often more severe at the time of relapse [131].

If the disease progresses to AP, the rate of fetal loss is increased (see Sect. 2.2.7); however, not all patients had gallstones. Also, the majority of patients with complicated gallstone disease who do not undergo antepartum cholecystectomy often have recurrent postpartum symptoms within 3 months postpartum. When appropriate, antepartum or early postpartum cholecystectomy is recommended to minimize symptom recurrence and unplanned hospitalizations [153].

Compared with patients managed surgically, nonoperative management was associated with a significantly higher rate of labor induction and PTD requiring neonatal intensive care [131], fetal death rate [151], and spontaneous abortion rate of 12% in the first trimester [8]. The effects of any medical intervention on fetal mortality have to be considered in the context of certain preexisting background risks that are common to all pregnancies. These include a 3% risk of birth defects, 15% for miscarriage, 4% for prematurity, 4% for growth retardation, and 1% for mental retardation or neurological developmental problems. Maternal nutrition per se is an important cause of PTL (see Sect. 23.3.4).

The patients treated conservatively had a higher rate of pregnancy-related complications

(36%) in comparison with the group treated with LC including a high incidence of multiple hospital admissions [135, 154]. In a prospective study of 122 pregnant patients with symptomatic gallbladder disease, 56.5% of patients failed conservative treatment [149].

Among the 69 patients who had LC with or without ERCP, there was no fetal morbidity or mortality [149]. A model suggested that LC is better than conservative treatment for pregnant patients presenting with symptomatic biliary diseases in the first and second trimesters (with an average gain of 4 quality pregnant weeks per women if treated with LC) [151]. Even in the third trimester of pregnancy, LC can be carried out safely without fetal morbidity [155, 156]. Eventually, symptoms of biliary colic or evidence of acute cholecystitis in late third trimester could be treated medically and postpartum LC performed with a comfort of a nonpregnant patient. Medical advances over the last several decades shifted the management toward a multidisciplinary and minimally invasive approach. Interventional radiology, ERCP, and LC are commonly employed, but their timing and indications need to be properly defined.

The maternal and neonatal advantages of operative treatment are [132]:

- Lower consumption of medications
- Lower hospital stay and number of hospitalizations
- Lower incidence of potential life-threatening complications:
  - Perforation
  - Biliary sepsis
  - Peritonitis
- Lower incidence of biliary AP
- Lower incidence of spontaneous abortions, PTL, and PTD

Open Versus Laparoscopic Cholecystectomy

On the basis of comparison of LC with OC, it is difficult to recommend any particular treatment because these studies did not specifically look at the physiological effects of pneumoperitoneum or CO_2-induced acidosis on the fetus during LC or the effects of uterine manipulation during OC [30, 133, 157, 158]. There was no significant difference in maternal and fetal outcome (6.74% PTDs in the LC group compared with 2.90% in the OC group). The absence of significant morbidity and mortality with the LC [30, 31] is a good prognostic parameter [149]. The largest study estimated a rate of 7% for fetal mortality and trimester recurrence rates of 55%, 55%, and 40% for nonoperative management. The rate of emergent surgery following nonoperative management was 19.5%. For LC the aggregate data suggest a fetal death rate of 2.5% [151].

LC in pregnant women provides all of the advantages of laparoscopy: significantly reduced hospitalization, decreased narcotic use, and quicker return to a regular diet [133, 135]. Other advantages of LC include less manipulation of the uterus (and less possibility of premature uterine contractions) and detection of other pathology if present [157]. It also decreases the possibility of postoperative deep vein thrombosis because of improved early mobility in such patients. As in nonpregnant population, if LC cannot be completed successfully, conversion to OC is mandatory [159]. Compared to OC, LC carries a decreased risk of spontaneous abortion in the first trimester and PTL in the third trimester [19].

In an attempt to overcome the potential adverse effects of pneumoperitoneum on the fetus, gasless laparoscopic surgery (GLS) has been developed. GLS in pregnancy has comparable outcomes to conventional CO_2 laparoscopy, but it is associated with some advantages. Hypercarbia and increased intraperitoneal pressure due to CO_2 insufflation are avoided (see Chap. 22). Up to 2017, only six cases of GLS cholecystectomy during pregnancy were published [160, 161].

LC has significant advantages in all outcomes measured compared to OC (Fig. 2.6). High volume surgeons have better outcomes in pregnant population than low volume surgeons (Fig. 2.7). Only 10.7% of pregnant patients underwent OC in the United States between 1999 and 2006 [162]. Conversion rate to OC in pregnancy in Australia is 13% [163].

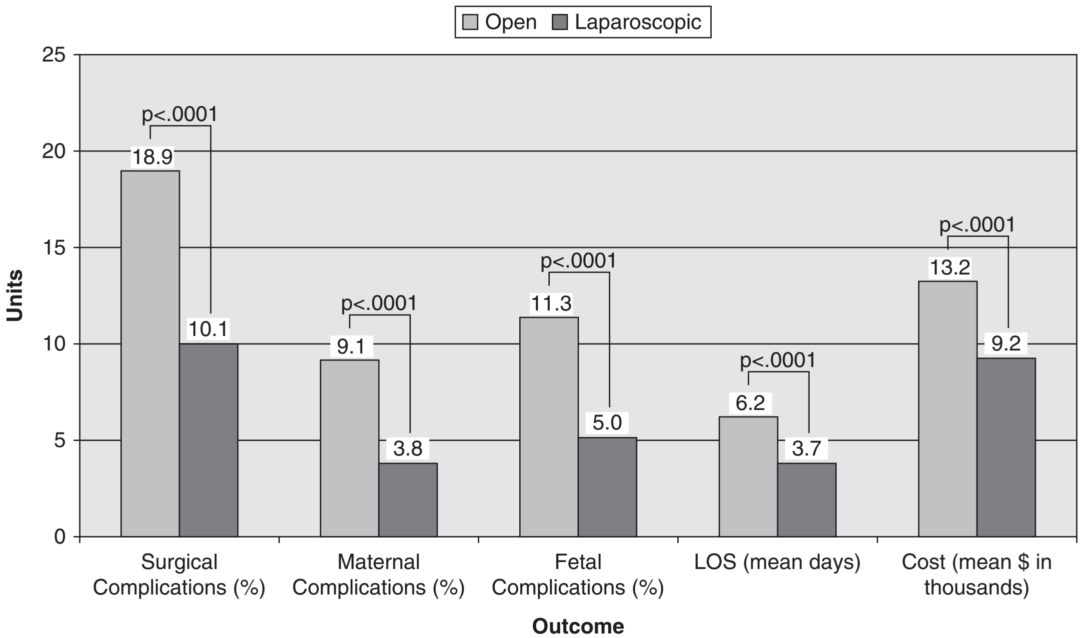

Fig. 2.6 Outcomes after cholecystectomy in pregnant women based on the type of procedure. *LOS* length of stay. Reproduced with permission from [162]

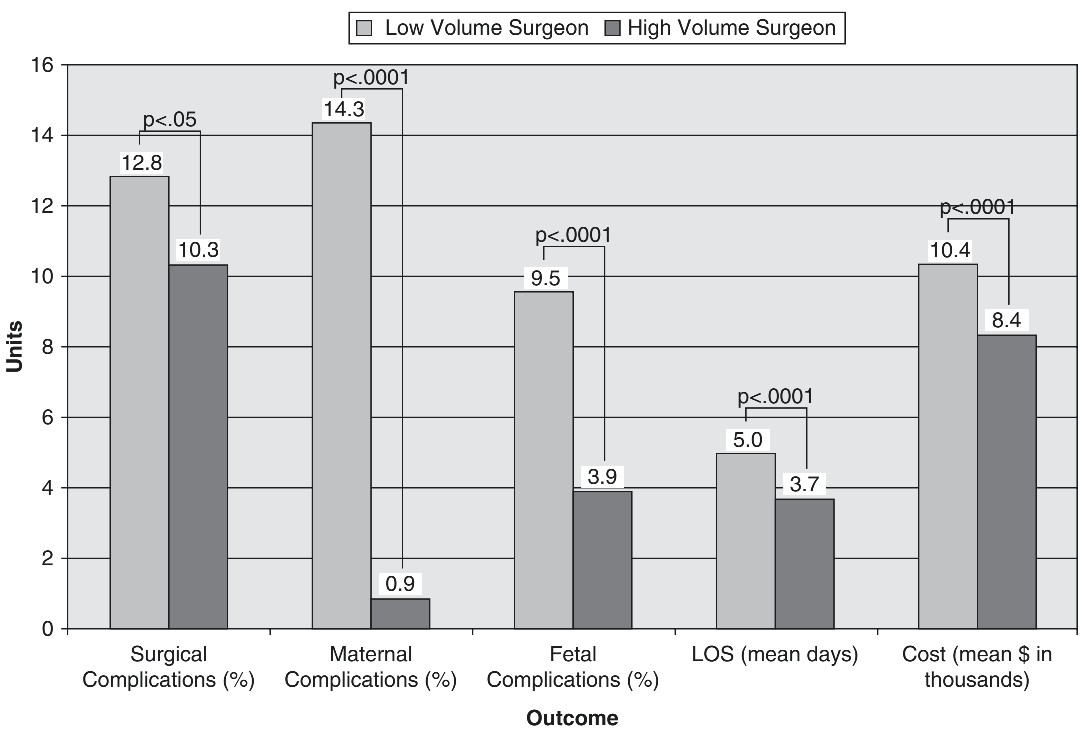

Fig. 2.7 Outcomes after cholecystectomy in pregnant women based on surgeon volume. *LOS* length of stay. Reproduced with permission from [162]

> Laparoscopic cholecystectomy is the treatment of choice in the pregnant patient with gallbladder disease, regardless of trimester [164].
> *SAGES Guidelines 2007*

Contraindications for Laparoscopic Surgery

Contraindications for laparoscopic surgery in pregnancy are principally the same as in non-pregnant population [165]:

Absolute Contraindications

- Hypovolemic shock, massive bleeding, or hemodynamic instability
- Severe cardiorespiratory disease
- Uncontrolled coagulopathy

Relative Contraindications

- Peritonitis
- Portal hypertension
- Multiple previous procedures/extensive intra-abdominal adhesions

2.1.8.5 Specific Considerations

Symptomatic Cholelithiasis in Diabetic Pregnant Patient

The serious consequences of cholelithiasis in diabetics are well established. There is only one article published with the analysis of a diabetic subgroup of pregnant patients with symptomatic cholelithiasis. A total of 35.8% of the patients had established diabetes mellitus. This is greater than the finding in general population of gallstone patients, among whom diabetes mellitus is only 11.1% [166]. This may suggest that patients with diabetes have a greater tendency to symptomatic gallstones in pregnancy. A more plausible explanation is that diabetic patients, educated to the tendency of diabetes mellitus to exacerbate the seriousness of many illnesses and already accustomed to the hospital, sought medical attention more often than the nonpregnant patients. The suggestion is to perform LC during pregnancy in the diabetic patient even if biliary colic is present.

Cholecystitis in IVF Pregnancy

The number of IVF pregnancies is constantly increasing (see Chap. 1); therefore, it is expected that the number of cases with acute cholecystitis during IVF pregnancy will also increase, especially because patient during assisted reproduction is exposed to higher doses of female hormones which are known risk factors for the genesis and progression of biliary sludge and stones. Currently, there are only two cases of LC in IVF pregnancy [167, 168]. There were no intra- or postoperative complications, and postoperative recovery of mother and baby was uneventful. For thromboprophylaxis, see Sect. 2.1.8.7.

Spontaneous Biliary Tract Perforations

Biliary tract perforations are unusual causes of peritonitis in pregnancy. The symptoms and signs are often nondiagnostic, and diagnosis may be delayed with possibly fatal consequences [169]. Gallbladder or CBD perforations as a cause of peritonitis in pregnancy have been rarely reported in the literature, and their exact incidence in pregnancy is unknown.

Gallbladder Perforation

Even when the gallbladder perforates, the usual outcome is a local abscess, on account of the adhesion that forms between the gallbladder, the greater omentum, and the parietal peritoneum [170]. Although gallbladder perforation has been reported to occur in 3–10% cases of acute cholecystitis in adults, free gallbladder perforation into the peritoneal cavity is even rarer, occurring in only 0.5% of the patients undergoing conservative management for acute cholecystitis. Risk factors for gallbladder perforation in adults include age greater than 60 years, immunosuppression, steroid use, and severe systemic disease [169]. The initiating event in the majority of these patients is impaction of the stone leading to epithelial injury and ischemia due to distension of the gallbladder. The site of perforation is either at the fundus, which is farthest away from the blood supply, or less commonly at the neck from the pressure of an impacted stone [171].

Perforation of the Common Bile Duct

Spontaneous perforation of the CBD is even a rarer event in adults, with only 45 cases reported [169, 172]. Bile duct perforation is most commonly described in infants related to congenital biliary system anomalies. As early as 1882, Freeland [173] reported the first case of extrahepatic biliary system rupture in an adult (diagnosed at autopsy), an entity that was subsequently first described in pregnancy by Hogan in 1957 [174], and currently there are only ten cases published in pregnancy [174–182], seemingly a high number compared to general adult population.

Pathogenesis, Diagnosis, and Treatment

Although the pathogenesis of spontaneous biliary perforation in the adult is poorly understood, recognized mechanisms include the following: calculous perforation at the site of impaction; calculous erosion without impaction; increased canalicular pressure due to obstruction by tumor, stone, or spasm of the sphincter of Oddi; intramural infection; mural vessel infarction leading to mural necrosis; or rupture of a biliary tract anomaly such as cyst or diverticulum [180]. The obstruction leads to an increase in intraductal pressure. This leads to dilation of the biliary tree and subsequent stasis and infection, ascending cholangitis, and thrombosis of intramural vessels. The end result is necrosis and perforation of the duct wall. Additional postulated cause is hemodynamic changes associated with higher pressure in the vena cava during pregnancy. Overall, 70% of cases are related to calculi in pregnancy [179].

Since this condition is unusual during pregnancy, accurate diagnosis and treatment may be delayed resulting in perinatal morbidity and mortality. Abdominal paracentesis is helpful in the diagnosis of biliary peritonitis. It is extremely difficult to diagnose it preoperatively, but free fluid in the abdomen with signs of acute abdomen and elevated liver function test should raise suspicion [178].

The surgical management of gallbladder perforation consists of cholecystectomy, copious irrigation, and drainage of the abdominal cavity [169]. Recommended treatment for CBD perforation includes cholecystectomy and decompression of the biliary tree in the form of CBD exploration with T-tube drainage in cases of small perforations. Roux-en-Y biliary-enteric anastomosis is indicated if the ductal disruption is large [180]. If CBD perforation is detected during diagnostic evaluation, endoscopic CBD stent placement followed by immediate or delayed biliary surgery (if necessary) is indicated [182]. If the general or hepatobiliary surgeon is not reachable in the emergency setting, subhepatic drainage with several large-diameter drains is recommended, and the patient is transferred to adequate surgical facilities [178].

2.1.8.6 Surgical Procedures

Open Cholecystectomy

There are two skin abdominal wall incisions used as in nonpregnant population:

- Right subcostal incision
- Upper midline incision

Both incisions are well known and performed in standard fashion, and the technique could be found in any abdominal surgery textbook or atlas. As in any other operation during pregnancy, it is important to eliminate or minimize uterine manipulation to minimize the possibility of uterine contractions and possible PTL or spontaneous abortion depending on the trimester of the operation. A midline incision is preferred if CS should be performed due to obstetric indications.

Laparoscopic Cholecystectomy

Decades ago, LC during pregnancy was considered as a relative contraindication, mainly because of the lack of knowledge of the effects of CO_2 to the fetus. Fear of surgical treatment was based on the potential risk of abortion or malformations if done during the first trimester or PTL when done in the last one. Direct uterine trauma, decreased uterine blood flow due to the pneumoperitoneum, and toxic narcotics drugs were suggested as possible causes of fetal morbidity (see Chaps. 21–23).

The first published case of LC on a 31 weeks' pregnant patient was in 1991 by Pucci and Seed [183]. Several series of LC for the management of cholecystitis have shown no negative side effects on the fetal outcome [184–186]. Up to 2008, there are 277 reported cases of LC in pregnant patients in the English literature. The data from these reports are retrospective, uncontrolled, and unblinded and surely represent only a fraction of the pregnant women who have undergone LC. Nevertheless, these data provide the best evidence available to determine how to treat a pregnant woman with biliary tract disease [151]. Potential advantages of LC in the pregnant patient include decreased fetal depression due to lessened postoperative narcotic requirements, lower risks of wound complications, and diminished postoperative maternal hypoventilation. There is an almost significantly lower incidence of premature contractions ($p = 0.057$) in LC compared to OC group [158]. The only significant differences between the LC and OC groups were that patients underwent LC at a mean of 5 weeks of gestation earlier than those who had OC and the serum alkaline phosphatase was significantly higher in the open group. In a small case–control study by Curet et al., 12 LC were compared with 11 OC. There were no spontaneous abortions or episodes of premature labor in the LC group and one PTL in the OC group [133]. No PTDs occurred after first-trimester LC in many studies [19, 157, 187].

> LC can be performed safely in the first trimester without an increase in maternal or fetal complications, and there is no need to defer surgery until the second trimester [188].

Third Trimester

When nonemergent LC is necessary, the recommendation is to perform it in the second trimester. In the second trimester, organogenesis is complete, and the risk of spontaneous abortion as seen in the first trimester and the risk of spontaneous labor as in the third trimester are significantly reduced [151, 189, 190]. The third trimester, however, poses certain potential difficulties mainly in terms of the diminished working space available owing to the enlarging uterus, the risk of injuring the uterus, and the perceived risk for excessive manipulation of the gravid uterus leading to PTL. The most serious complication of the uterine injury includes that of fetal loss owing to pneumoamnion resulting from inadvertent injury during Veress needle insertion for pneumoperitoneum [191]. A near-term gravid uterus makes an LC technically impossible, and near-term pregnancy is the only absolute indication for OC [21, 140]. The specific problem poses patients with an indication for elective or emergent CS. After CS, depending on the severity of cholecystitis, one can decide between OC and LC and conservative treatment with elective cholecystectomy after 6 weeks. In 1991, Pucci and Seed published a case report of a successful LC in 31 weeks pregnancy [183]. PTD rate is similar in both the LC and OC groups during the third trimester. There were no fetal losses, uterine injuries, or spontaneous abortions in the LC group. Most reports suggest the safety of LC in pregnant women including the third trimester [151, 157, 187, 189, 190, 192, 193]. The literature analyzing 30 years period found no reports of LC or OC in the third trimester that had not resulted in a viable birth [192]. It should be stressed that appendicitis and cholecystitis as specific pathologies have a different influence on uterine irritability possibly due to (1) different nature (different bacteria) of localized peritonitis and (2) different distance between inflamed organ and uterus (the appendix is commonly in contact with the uterus). The upper gestational limit for LC is not defined, and several series between 28 and 34 weeks of pregnancy were successfully performed [187, 189].

Open (Hasson) Technique

According to an NIH statement from 1993, patients in the third trimester of pregnancy should generally not undergo LC, because of the risk of damage to the uterus and the difficulty presented by the large and gravid uterus, which can obstruct safe access to the abdomen and gallbladder fossa [194]. Some suggested a gestational age limit of 26–28 weeks for laparoscopic surgery in general [195]. Although in the past

Society of American Gastrointestinal Endoscopic Surgery (SAGES) recommended an open technique of initial port placement, in a revision of their guidelines (the year 2007), suggestion is that the initial access could be safely accomplished by open (Hasson) technique, Veress needle, or optical trocar technique, the location of trocar placement being adjusted according to the fundal height, earlier incisions, and experience of the surgeon [196].

When Veress needle is used for insufflation, it could be safely carried out by inserting it in either the left or the right upper quadrant in the midclavicular line approximately 1–3 cm below the costal margin [189, 197]. After inserting a 5 mm trocar at this site, a 5 mm camera is then used to guide the insertion of the rest of the ports under direct vision [189].

The usual umbilical port for the camera is placed few centimeters cephalad beyond the fundus of the gravid uterus in the midline usually in supraumbilical position. The insufflation pressure is 12–15 mmHg. A pressure of 15 mmHg should not be of concern as in the third trimester, as at times the uterine pressures can reach very high during spontaneous intermittent contractions [189]. Currently, optical trocars or the so-called direct vision initial ports have become available. These can be used with or without pneumoperitoneum under direct vision.

Single Incision Laparoscopic Surgery

There is an increasing rate of single incision laparoscopic surgery (SILS) in general population. This is translated in pregnant population, and more and more cases are performed by this approach. All trocars are located through transumbilical port through single incision eliminating abdominal wall injury through separate stab incisions (Fig. 2.8). This method can be used during the first and second trimesters. There are no recommendations and guidelines published up to date.

Gasless Laparoscopy

To eliminate the possible influence of CO_2 pneumoperitoneum on the fetus, some use laparoscopy without the use of pneumoperitoneum [160, 161]. This method is not well accepted in pregnant as in nonpregnant population.

Fig. 2.8 SILS cholecystectomy with a 10 mm and a low-profile, 5 mm cannula at the umbilicus. Reproduced with permission from [198]

Local Anesthesia

Local anesthesia with prolonged duration of action could be utilized in port sites for improved postoperative analgesia, which minimizes narcotic requirements after surgery.

2.1.8.7 Perioperative Management

See Chap. 21.

2.1.8.8 Prevention and Treatment of Preterm Labor

See Chap. 23.

Duration of Hospitalization

LC patients were able to tolerate clear liquids 0.6 days sooner and regular diet 0.3 days sooner than OC patients [131]. There is a significant reduction in hospitalization time for LC in comparison with OC (6.2 days vs. 3.7 days) [133, 162]. Mean hospitalization was 2–4.5 days for acute cholecystitis treated with LC [149, 193] and 3 days for CBD exploration [149].

2.1.8.9 Surgical Considerations in the Postpartum Period

The abdominal wall also undergoes significant change during pregnancy, with muscle tone reduction and skin elasticity to accommodate the enlarging uterus. The abdominal wall tone remains lax for several weeks postpartum, returning to a near-nonparous level in 6–7 weeks. The hallmarks of the acute surgical disease, abdominal guarding and rigidity, do not occur during the early puerperium. This single feature of the puer-

perium is responsible for confusion and delay in proper surgical diagnosis. Puerperal changes in blood components may be confusing as well. During the first 10–14 days of the puerperium, WBC counts of 20,000–25,000/mm^3 are not unusual; there is also a predominant increase in neutrophils. The erythrocyte sedimentation rate may increase to 50–60 mm/h. Reliance on either the erythrocyte sedimentation rate or the WBC count for the diagnosis of acute infection may be misleading. The postpartum patient can be operated upon without the added concerns of the fetus; however, several unique characteristics apply to this group. In the early postpartum period, the enlarged uterus is a potential technical factor. In the CS patient, the challenges of a recent surgical incision must be considered. Safe access to the peritoneal cavity and ultimate protection of the recent incision are important factors. Finally, unique features of the biliary tract disease during the postpartum period may require special consideration. Any conservative treatment course is hampered by these patients' strong desire to minimize the number of hospital days, recurrent symptoms, and disability. Physiologically, postpartum patients are still recovering from pregnancy and childbirth. In addition, separation from a newborn, combined with varying degrees of labile emotions related to the postpartum state, serves to accentuate the usual psychological stresses of illness. If early laparoscopy can be applied to this group, the benefits will be even greater than that reported for the general population.

The enlarged uterus does not hamper exposure, even in the first week. At the time of surgery, the uterine fundus is below the umbilicus. This is consistent with technical success and good exposure in pregnant patients undergoing laparoscopy during the first and second trimesters [133]. There were no adhesions encountered in the CS group. The course of the procedure and recovery was identical to the remainder of patients.

The final unique consideration in the postpartum patient is the presence of a healing abdominal incision after CS. There are no published studies on outcomes for recent abdominal incisions subjected to early pneumoperitoneum. Pneumoperitoneum is limited to 10 mmHg pressure in the CS patients. This may prevent undue mechanical strain on the healing wound, though there were no controls with the standard (15–16 mmHg pressure) for comparison. It seems prudent to utilize the minimal intra-abdominal pressure necessary for adequate exposure in these patients. Although evidence suggests fascial separation, if present, occurs early, it remains to be seen what long-term status these incisions will achieve. No hernia has developed in these patients with a follow-up to 5.5 years [199].

Gallstone-Related Hospitalization During the First Postpartum Year

Gallbladder disease is a leading nonobstetric cause of hospitalization in the first-year postpartum. Seventy-six percent were diagnosed with uncomplicated cholelithiasis, 16% with AP, 9% with acute cholecystitis, and 8% with cholangitis. Seventy-three percent of hospitalized women underwent cholecystectomy and 5% underwent ERCP. On multivariate analysis, independent risk factors for hospitalization included maternal race, age, being overweight or obese prepregnancy, pregnancy weight gain, and estimated gestational age [7].

2.1.8.10 Combined or Consecutive Operations During the Same Pregnancy

As previously reported, one unusual patient required two separate laparoscopic operations during the same pregnancy: cholecystectomy at 6 weeks gestation and later at 20 weeks appendectomy and reduction of an ovarian torsion. Another patient, at term, underwent combined planned CS and LC. The cholecystectomy was performed first because it was felt that it would be safer to conduct a cholecystectomy in a stable patient prior to any significant bleeding potentially encountered with child birth [200]. Two additional benefits are (1) there is no high intra-abdominal pressure after CS and (2) it is easier to make extended median laparotomy if LC fails, to perform combined OC and CS.

2.1.9 Prognosis

2.1.9.1 Maternal Outcome

Maternal Mortality

Pregnancy does not seem to increase the severity of gallstone complications. Most (60–69%) gallstones are asymptomatic during pregnancy [4, 12, 31, 104]. Prognosis after cholecystectomy during pregnancy is excellent. Most authors declare that there is no maternal mortality and most complications include wound infections [149, 201]. Reports of 310 patients comparing conservative with surgical management, all patients were initially treated conservatively. No maternal mortality was reported in either group [202].

Maternal Morbidity

Pregnant women who underwent cholecystectomy compared with not operated pregnant women hospitalized with biliary tract disease had significantly lower maternal complication rates (4.3% vs. 16.5%) [162]. Compared with non-pregnant women undergoing cholecystectomy, pregnant women had higher rates of unadjusted surgical complications (10.7% vs. 9.6%) and longer unadjusted mean length of hospital stay (3.5 vs. 2.9 days) [162]. There was no significant difference in rates of ERCP or intraoperative cholangiogram, the urgency of admission, comorbidity, income distribution, hospital size, or annual volume of cholecystectomies [162].

2.1.9.2 Fetal Outcome

Earlier studies on pregnancy-related gallbladder disease showed fetal loss of 12–15% [6, 203, 204], some even 24% after cholecystectomy [205]. If one of four patients with fetal loss (of total 17 patients) is excluded due to postoperative peritonitis (cholecystectomy and appendectomy were performed during initial operation), then the fetal rate is 18%. At that time, 10% of all pregnancies ended in abortion [206]. The causal relationship to surgery was not clear at that time, because of the varied time lapse between surgery and abortion. Even in 1997, a study in *British Journal of Surgery* recommended conservative treatment [20].

All of the placental and amniotic complications occurred in patients undergoing cholecystectomy and were with LC. Additionally, the incidence of placental/amniotic complications was statistically higher in those undergoing cholecystectomy compared with appendectomy [207]. The etiology of this association is not clear especially because others state no fetal morbidity or mortality [149]. The incidence of PTDs with conservative management was 3.5% compared with 6.0% in patients receiving surgical treatment. Fetal mortality in the conservative group was higher (2.2%) than in an operated group (1.2%) [202], with similar rates of PTD after OC (10%) and LC (11.9%) and no fetal loss [157]. In a subsequent series from the same institution, there was an increase in PTD and fetal loss, but not statistically significant for LC (20% and 3%, respectively). This increase cannot be attributed only to operation because (1) it may reflect the increase in PTD rates for all pregnancies, (2) there is an increase in PTD rates reported nationally, and (3) PTD occurred an average of 3 months after the procedure – therefore, it is difficult to attribute PTD solely to the procedure and not to other postsurgical patient variables [187]. Pregnant women who underwent cholecystectomy compared to medically treated pregnant women with biliary tract disease had significantly lower fetal complication rates (5.8% vs. 16.5%) [162]. Palanivelu et al. described 9 LCs with no fetal loss [201].

2.2 Common Bile Duct Stones and Acute Cholangitis

2.2.1 Incidence

1/1200 pregnancies are complicated by CBD stones [208] which have been observed in 10–12.5% of pregnant women undergoing cholecystectomy [150, 209] and account for 7% of cases of jaundice in pregnancy [9]. In some studies biliary AP is the most common form, affecting up to 70% of patients with AP during pregnancy [210]. The wide variations in incidence are influenced by the prevalence of its most

important etiological factors – gallstone disease, hypertriglyceridemia, and alcohol consumption. While biliary AP complicated 1/3300 pregnancies in Dallas, Texas [211], in Southern California 1/1500 women were affected [210].

2.2.2 Risk Factors

Due to a small number of patients in pregnancy, specific risk factors are not known. Known etiologies share the same pathophysiology as in nonpregnant women. Risk factors are the mostly the same as the risk factors for gallbladder stones in pregnancy (see Sect. 2.1.3).

2.2.3 Clinical Presentation

Clinical presentation of pregnant patients with CBD stones is the same as in nonpregnant population. Classical symptoms include abdominal pain, jaundice, nausea, vomiting, and itching. If painless icterus without elevated body temperature is present, then CBD stones or periampullary tumor should be suspected, or if painful with fever and chills, then acute cholangitis is the most probable diagnosis. The additional diagnostic challenge exists due to pregnancy-related hepatobiliary diseases which should be included in differential diagnosis (see Sect. 2.2.4).

Clinical presentation of biliary AP is similar to AP of any cause and is described in detail in Chap. 3. The symptoms of gallbladder disease can be present or can precede the clinical presentation of biliary AP. The symptoms include abdominal pain (colicky or stabbing) which may radiate to the right flank, scapula, and shoulder. The onset of pain is rapid, with maximal intensity in 10–20 min. Pain is steady and moderate to severe. Band-like radiation of the pain to the back occurs in half of the patients. Other symptoms of gallbladder disease include anorexia, nausea, vomiting, dyspepsia, low-grade fever, tachycardia, and fatty food intolerance [211], some of which cannot be distinguished from symptoms of AP itself.

2.2.4 Differential Diagnosis

There are several entities that should be included in differential diagnosis of CBD stones and cholangitis. Most of them could be easily excluded after abdominal ultrasound or MRCP. The two entities found in pregnancy are presented in more detail for easier determination of definitive diagnosis: intrahepatic cholestasis of pregnancy and acute fatty liver of pregnancy. Acute cholecystitis can develop along with CBD stones.

2.2.4.1 Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) usually occurs rarely before 25 weeks and disappears spontaneously after delivery. The prevalence of ICP varies widely [212]. The highest frequencies have been reported in Bolivia and Chile. In Chile, the prevalence in 1974–1975 ranged 11.8–27.7% according to the ethnic origin [213]. For unknown reasons, the prevalence has more recently appeared to decrease (4.0–6.5%) [213, 214]. In the United States, the prevalence ranges 0.3–5.6% according to the ethnic origin [215, 216]. The prevalence in Europe is about 0.5–1.5% [212]. Generally, ICP is more common in twin pregnancies [217].

Pruritus is the main symptom, initially on the palms and soles progressively spreading to other parts of the body and increasingly becoming more persistent. It is more severe at night and disturbs sleep. Pruritus usually disappears within the first few days following delivery [213]. The patient may also be instructed to estimate the intensity of pruritus on a 100 mm long visual analog scale [218]. These scales for monitoring the intensity of pruritus are particularly useful to evaluate the effect of medical treatment on this subjective symptom. The clinical examination findings are normal except for evidence of scratching. Fever, if present, is usually caused by an associated urinary tract infection. The prevalence of jaundice varies from 17 to 75% [219–221]. The greater frequency of jaundice in some studies may be a consequence of concomitant urinary tract infection [222]. ICP with jaundice but without pruritus is rare [223]. Patients do not experience abdominal pain or encephalopathy.

Ultrasonographic examination reveals no dilatation of the biliary tract but may show gallstones. Measurement of serum ALT activity is a sensitive test for the diagnosis of ICP. Patients with ICP frequently exhibit very significant increases in serum ALT activity that suggests acute viral hepatitis, which should be ruled out with serologic tests [223]. Liver histology does not reveal necrotic lesions, and the ALT elevations may be secondary to an increase in membrane permeability. The serum GGT is normal or slightly increased [223]. The serum bile acid concentrations are increased and may be the first or only laboratory abnormality [223]. A relationship between maternal serum bile acid levels and fetal distress has been found, and evaluation of the serum bile acid concentration has been suggested as a mean of fetal assessment in patients with ICP [218]. However, no consensus has been reached concerning the usefulness of evaluating the serum bile acid concentrations in the obstetric management of patients with ICP [224]. Little or no correlation has been found between the serum total bile acid concentrations and other liver test values [223]. The serum bile acid concentration and serum ALT activity decrease rapidly after delivery and, as a rule, normalize in a few weeks. The measurement of serum glutathione S-transferase, a maker of hepatocellular integrity, has been proposed to distinguish ICP from "benign pruritus gravidarum" [225], but its use in routine is limited. The prothrombin time is usually normal. It may become abnormal in severe cholestasis with jaundice or in patients who have been treated with cholestyramine. The abnormality is caused by vitamin K deficiency, which should be anticipated and treated before delivery to prevent hemorrhage. Such therapy contributes to a good maternal prognosis. ICP has been found associated with preeclampsia [226] or acute fatty liver of pregnancy (AFLP) [227] (see Sect. 2.2.4.2). Liver biopsy is rarely necessary for the diagnosis. Histopathology is characterized by pure cholestasis, sometimes with bile plugs in the hepatocytes and canaliculi, predominantly in zone 3. Inflammation and necrosis are not usually observed, and the portal tracts are unaffected [228].

2.2.4.2 Acute Fatty Liver of Pregnancy

AFLP was distinguished as a specific clinical entity unique to pregnancy in 1940 by Sheehan [229]. AFLP is rare with an incidence in the range of 1/7000–1/20,000 deliveries [230, 231]. As a rule, AFLP is a disease of the third trimester that may occur during any gestation and is not always diagnosed prior to delivery. The frequency of twin gestations is increased among patients with AFLP [231], and 7% of triplet pregnancies have been reported to be complicated by AFLP [232]. The most frequent initial symptoms are nausea or vomiting, abdominal pain (especially epigastric), anorexia, and jaundice [233]. In the past, jaundice was almost always seen during the course of the disease, but because of earlier diagnosis, prompt delivery, and the diagnosis of milder cases, there are affected patients without jaundice. The size of the liver is usually normal or small. Patients with AFLP rarely have pruritus. Hypertension and proteinuria which are the main signs of preeclampsia are found in up to half the patients [234, 235]. In severe forms, patients may demonstrate asterixis and encephalopathy, with or without coma. Esophagitis and Mallory-Weiss syndrome related to severe vomiting have been reported, as well as bleeding secondary to these esophageal lesions. Genital bleeding is frequent. These hemorrhages are exacerbated by associated coagulation disorders. Ascites may be present and is partially related to portal hypertension. Polyuria and polydipsia (without diabetes mellitus) have been noted in about 5% of patients with AFLP [234] and are almost pathognomonic symptoms in this setting of liver disease in pregnancy. AP is a rare but a potentially severe complication (see Chap. 3). The serum aminotransferase levels are raised, but usually, the level is not as high as in acute viral hepatitis. The bilirubin level is almost always increased. Patients may demonstrate hypoglycemia, which is uncommon in other liver diseases unique to pregnancy. In severe cases, the prothrombin time is increased and the fibrinogen level decreased. These coagulation disorders are caused by hepatic insufficiency, disseminated intravascular coagulation, or both. A low platelet count is usual in AFLP and is not always

associated with other signs of disseminated intravascular coagulation. Thrombocytopenia may be the most striking laboratory feature and normalizes spontaneously after delivery. The diagnosis of AFLP should always be considered when thrombocytopenia occurs during late pregnancy and should always prompt the performance of liver function tests. Renal failure (mainly functional) and hyperuricemia are usual. Ultrasonography of the liver may show increased echogenicity. Abdominal CT may be useful for the diagnosis, and a liver density that is lower than usual may be demonstrated by Hounsfield unit values in the liver that is equal to or lower than those in the spleen [233]. The findings on imaging studies may be normal; however, a study showed that the findings on abdominal CT, which is more sensitive than ultrasonography, were normal in half of the patients with AFLP [236]. These complementary examinations should not delay delivery, particularly in severe cases, in which diagnosis can usually be highly suspected on clinical grounds with routine blood tests (serum liver tests, glycemia, creatininemia, electrolytes, uricemia, full blood count including platelets, prothrombin time). Liver biopsy is the best way to confirm the diagnosis of AFLP, but because it is invasive, it is not always performed. Also, noninvasive procedures can demonstrate fat in the liver and exclude other liver diseases, such as viral hepatitis. Nevertheless, a liver biopsy may be useful in atypical cases, especially if the appropriate treatment (delivery) is being delayed. The overall architecture of the liver is not altered. The characteristic picture is a microvesicular fatty infiltration of the hepatocytes, which are swollen. The droplets are minute and surround centrally located nuclei so that the cytoplasm has a foamy appearance. The droplets stain with oil red O, which is specific for fat. Electron microscopy confirms the presence of fat droplets [237]. A stain specific for fat or electron microscopy is useful for pathology confirmation of the diagnosis in patients with ballooning of the cytoplasm but no evident vacuolization [233]. Therefore, whenever AFLP is suspected, a piece of the liver biopsy specimen should be reserved before paraffin embedding and processed appropriately with special stains to confirm the presence of fat in the hepatocytes. The pathological changes normally reverse rapidly after delivery, and AFLP is not associated with progression to cirrhosis [235]. When AFLP was first described, it was considered fatal [229]. However, early diagnosis has dramatically improved maternal survival, and maternal mortality is currently the exception rather than the rule [238].

2.2.5 Diagnosis

2.2.5.1 Laboratory Findings

Liver tests in pregnant women with biliary AP are frequently normal. The transaminase levels are less than 5× the upper normal limits in 89% of patients and less than 3× the upper normal limits in 80% of patients. One possibility is that increased metabolism of maternal transaminases by the placenta leads to relatively normal maternal levels of liver enzymes [37].

2.2.5.2 Transabdominal Ultrasound

Ultrasound is the imaging method of choice for evaluation of the biliary system and is accurate in diagnosing cholelithiasis in 97% of cases [41, 114]. Its accuracy, however, is limited in the evaluation of the CBD (50%) and the pancreas (partial visualization in 60% with unremarkable findings) [119].

2.2.5.3 MRCP

MRCP is the best imaging option for definitive diagnosis of biliary diseases in pregnancy if abdominal ultrasound is not diagnostic. MRCP is rarely used due to the rarity of the disease and not widespread availability [119, 239, 240]. This imaging method is important because it can differentiate between CBD stones and Mirizzi syndrome (Fig. 2.4). Patient diagnosed as having Mirizzi syndrome undergoes surgery, and jaundice improves after cholecystectomy without endoscopic sphincterotomy or exploration of the CBD. This is especially important in pregnant population because this eliminates radiation exposure during pregnancy. Recent refinements in the technique and the development of 3D

MRCP sequences further improved MRCP, allowing the reconstruction of overlapping slices of less than 1 mm. With a reported accuracy close to 100% in determining the presence and level of biliary obstruction, MRCP has replaced diagnostic ERCP in many institutions, and the utilization of ERCP for diagnostic purposes is steadily decreasing.

2.2.5.4 ERCP

ERCP was first reported during pregnancy in 1990 by Baillie et al. for the treatment of complicated gallstone disease [241]. Guidelines on AP management in general population state that urgent therapeutic ERCP should be performed in patients with AP of suspected or proven gallstone etiology who satisfy the criteria for predicted or actual severe pancreatitis, or when there is cholangitis, jaundice, or a dilated CBD. The procedure is best carried out within the first 72 h after the onset of pain. All patients undergoing early ERCP for severe biliary AP require endoscopic sphincterotomy whether or not stones are found in the bile duct [242]. However, consideration should be given to extending the therapeutic indications for emergency papillotomy to mild and idiopathic types of gestational biliary AP. There are several important issues for the ERCP use in pregnancy discussed below.

Radiation

Clinicians may not be well informed of the facts relating to the use of diagnostic radiological studies in pregnancy. Lack of understanding of radiation effects on the fetus causes unnecessary anxiety in pregnant patients exposed to diagnostic radiation and may lead to unnecessary pregnancy termination. A study examining physician perceptions of teratogenic risk associated with undergoing plain radiography and CT during early pregnancy found that 3% of family practice physicians would recommend pregnancy termination after first-trimester CT and 0.5% following radiography in the first trimester; 12% were not sure of the need for pregnancy termination after radiography; and 19% were not sure about a CT scan examination. The same study reported that 8% of obstetricians would recommend pregnancy termination after first-trimester CT scan examination [243].

Hoffman and Cunningham in 1992 reported four pregnant women who underwent ERCP during the first trimester. Radiation exposure after appropriate abdominal shielding was calculated and found to be well below levels at which damage to the fetus can occur [244]. The amount of radiation used during ERCP is 18–310 mrad [245, 246]. The *American College of Obstetricians and Gynecologists* (ACOG) states that risks for fetal anomalies, growth restriction, or abortions are not increased with radiation exposure of less than 5 rad, a level above the range of exposure for diagnostic procedures [247]. Radiation risk is greatest during the first trimester. Fluoroscopy generally delivers a radiation dose of up to 20 rads/min but varies depending on the X-ray equipment utilized, patient positioning, and patient size. The fetus should be shielded during cholangiography. Other alternatives to fluoroscopy include intraoperative ultrasound and choledochoscopy. Recently more ERCP procedures are performed without fluoroscopy to eliminate the radiation risk [248, 249], mostly as a two-stage approach. Successful biliary drainage is done in the first ERCP which is mostly used during the third trimester when the completion of pregnancy is near. Biliary sphincterotomy with mainly small incision is recommended for first-stage ERCP, which will avoid biliary AP caused or aggravated by stent-induced pancreatic duct obstruction, and avoid dislodge or early falloff of the plastic stent due to the excessively large incision. Then after delivery, the second ERCP with the definitive extraction of calculi under fluoroscopic control is performed [248]. Even though the risks to the fetus during the second and the third trimester for radiation exposure are low, it is recommended to protect the uterus with a lead shield.

ERCP Techniques

Eliminating radiation exposure can be accomplished by cannulating the CBD with a sphincterotome over a guidewire that can be fixed in place, performing sphincterotomy, exchanging the sphincterotome for an extraction balloon

catheter over the guidewire, and sweeping the bile duct without a cholangiogram to extract any stones. The main criticism of this technique is that it provides no real-time information regarding the anatomy of the ductal system and documentation of stone clearance [249]. Another option is capturing fluoroscopic images with a videoendoscopy system providing safer ERCP procedure than using spot radiography [250]. The third option is sphincterotomy under ultrasound guidance and without any imaging technique [251]. The aspiration of the bile after deep cannulation enabled confirmation of selective CBD cannulation and endoscopic sphincterotomy without radiographic control. In one modification initial CBD cannulation is done with the help of a double-lumen sphincterotome, deep cannulation is achieved, and the bile is aspirated to confirm CBD position. After deep CBD cannulation, the guidewire is passed, and complete biliary sphincterotomy was done over the guidewire. In cases where deep CBD cannulation is not possible, after two attempts, the conventional sphincterotome is removed, and patients are subjected to needle-knife sphincterotomy. Once the biliary orifice is identified, a complete biliary sphincterotomy is performed using a conventional double-lumen sphincterotome after confirming the location inside CBD. After the biliary sphincterotomy, a Zag guidewire was left in place and a 7Fr double pigtail stent is placed in the CBD. Patients are kept nil orally for 6 h after the procedure, and i.v. fluids and i.v. cefotaxime 1 g bid are given for 1 day followed by oral antibiotics for 5–7 days. After delivery, all the patients are subjected to definitive ERCP. Biliary stents are removed, and cholangiogram is obtained. All small stones are removed with Dormia basket, and if large stones are retained, mechanical lithotripsy is used. Patients with multiple large stones are subjected to surgery [252]. Aspiration technique is used to avoid pancreatography, and fluoroscopy time should be as short as possible (<1 min) and spot radiographs avoided if possible [253].

When facing more invasive operative and interventional options – surgery or percutaneous transhepatic cholangiography – ERCP may be the best therapeutic option in the setting of pregnancy.

> ERCP in pregnancy tends to be safe for both the mother and the fetus, but the procedure should be largely restricted to therapeutic indications with additional intraprocedural safety measures [246].

Due to the ability of the amniotic fluid to conduct electrical current to the fetus, the grounding pad should be placed on the patient above the level of the uterus [245].

Sedation

See Chap. 21.

Contrast Agents

Among other considerations for ERCP in pregnancy, contrast agents that contain iodine, such as diatrizoate, have the potential to cause hypothyroidism in the baby. Risks may be minimized by using low concentrations of diatrizoate, especially the water-soluble form, thus limiting the number of intraductal injections and avoiding unnecessary pancreatography [254]. Guidelines for the use of contrast media during pregnancy are listed in Table 2.2.

ERCP in Diabetic Pregnant Patient

There is only one case report of ERCP in a diabetic patient on insulin therapy that was euglycemic during the procedure for obstructive jaundice due to residual CBD stones. The patient had ERCP 1 year ago for CBD stones with LC after 3 months [240].

Complications

In uncomplicated cases, amylase normalization occurs within 36–48 h [255]. In the non-pregnant patient, the risk of bleeding and AP is 1.3% and 3.5%, respectively. The complications in pregnancy consist mainly of post-ERCP AP (6–16%) [137, 256, 257], PTL, and post-sphincterotomy bleeding [245, 246, 256–258]. Some studies do not differentiate groups with biliary AP that underwent ERCP (pre-ERCP AP) and CBD stones. ERCP during pregnancy is technically exacting and should be attempted only by experienced biliary endoscopists [65, 150, 246, 253, 256].

Laparoscopic cholecystectomy and ERCP during pregnancy appear to be safe and justified. ERCP for the treatment of CBD stones and acute cholangitis in pregnancy is preferred to surgical approach [65, 150, 241, 246, 253, 256–258].

Several issues should be stressed. First, there is no randomized, controlled study comparing ERCP and open (or laparoscopic) surgery in view of the efficacy and safety. Second, ERCP is not the first-line treatment if CBD stones and acute cholangitis in pregnancy are due to the choledochal cyst (see Sect. 2.3).

2.2.5.5 Endoscopic Ultrasound

Endoscopic ultrasound (EUS), a semi-invasive procedure of the biliary tree, is rarely used as a definitive diagnostic tool for the identification of stones in the distal CBD. Mostly it is used before endoscopic retrograde cholangiopancreatography (ERCP) for therapeutic strategy or as a confirmatory tool after sphincterotomy stone extraction. It has been shown to reduce unnecessary interventions in patients with low or moderate probabilities for CBD stones [259].

When a CBD stone is suspected, EUS has a high positive predictive value nearing 100%, even for small stones ≤2 mm or sludge [259, 260]. EUS is considered the best imaging study to evaluate the CBD but requires expensive equipment, intravenous sedation, and technical expertise. It is superior to magnetic resonance cholangiopancreatography (MRCP), an imaging method providing a multiplanar large field of view images of the biliopancreaticoductal system [261].

EUS is appropriate prior to the consideration of therapeutic ERCP in patients where noninvasive imaging such as MRCP is not available, contraindicated, or inconclusive. There is no radiation exposure, and this is extremely safe apart from a minimal sedation-related risk. If a CBD stone is detected, an ERCP with sphincterotomy can be performed following the EUS during the same sedation.

2.2.6 Treatment

There is no consensus for the best treatment method in biliary AP in pregnancy. ERCP is safe in pregnancy, and biliary stenting can be performed [262]. Previous studies have shown low rates of PTL that were not significantly different from those of conservative therapy in patients undergoing preterm surgery or endoscopic intervention for simple bile stones.

2.2.6.1 Choledochoscopy

Choledochoscopy could be used during CBD exploration (open or laparoscopic) or after sphincterotomy. Wire-guided CBD cannulation with sphincterotomy and the removal of biliary stones or sludge can be performed without fluoroscopy. Choledochoscopy can confirm ductal clearance [263, 264]. If choledochoscopy is not available, an alternative approach is to use EUS-guided extraction balloon sweeps. The technique with SpyGlass Direct Visualization System (Boston Scientific, Natick, MA, USA) is presented. A 4.4 Fr sphincterotome is angled in the biliary orientation and a hydrophilic 0.35″ guidewire gently advanced into the major papilla resulting in bile flow around the guidewire. The sphincterotome is advanced over the wire, and aspiration of 10 ml of clear yellow bile confirmed the location within the bile duct. A biliary sphincterotomy is performed. Sweep with a 9 mm extraction balloon is done. The SpyGlass SpyScope was exchanged over the guidewire, and cholangioscopy directly visualized the CBD, common hepatic duct, and left and right intrahepatic ducts. Saline lavage through the cholangioscope flushes debris from the CBD into the duodenum. No fluoroscopy is needed. To date, seven pregnant patients undergoing SpyGlass cholangioscopy-assisted ERCP have been reported [263–265]. The use of non-fluoroscopy interventions may actually prolong the overall duration of the procedure due to learning curves and technical experiences of endoscopists and hence increases the risk, especially in difficult cases. Furthermore, in daily practice, non-fluoroscopy modalities are not often used.

Therefore, one should not hesitate to use fluoroscopy if required with the knowledge that limited radiation exposure is safe during pregnancy [246].

2.2.6.2 Laparoscopic Cholecystectomy After ERCP

There is no consensus whether LC should be performed after successful ERCP with stone extraction. There are several options.

Selective (Wait-and-See) Approach

In one study five patients underwent ERCP due to CBD stones, and two patients had developed cholecystitis. After LC the remainder of the pregnancy was uneventful [65]. All five patients had healthy babies at term with vaginal delivery. In nonpregnant patients, the prospective randomized trial demonstrated a conversion rate of 55% in patients who were allocated to a wait-and-see policy after ERCP and a 23% conversion rate in the elective LC group. This result implies that LC after ERCP is mandatory (see next section).

Mandatory Cholecystectomy

The numbers of emergency department visits, recurrent biliary symptoms, and hospitalizations are significantly higher in the conservative treatment group compared to the active intervention group (cholecystectomy and/or ERCP). Therefore, an elective LC after ERCP is safe to approach during pregnancy [266]. In practice, some strongly advocate an LC within 6 weeks of the initial biliary event. In pregnant population, successful ERCP was reported in six women between 6 and 30 weeks of gestation with symptomatic acute cholangitis or AP, without radiation exposure or major maternal complications [249]. No post-ERCP complications occurred. Two patients required cholecystectomy later, one in the postpartum period and the other 5 weeks post-ERCP. Two infants were born at term without complications. Two infants were born prematurely at 35 weeks, one with significant growth restriction and pulmonary complications and one without developmental problems or complications. Patients presenting in the first or second trimester should, if possible, undergo LC in the second trimester when the risk of anesthesia and premature labor are the lowest. In advanced third trimester, LC could be postponed after delivery.

There are no studies in pregnant population defining the interval between ERCP and LC. In nonpregnant population, there is an increased risk of conversion to open procedure in the period of 2–6 weeks after ERCP. Higher conversion rate could be that ERCP leads to an inflammation around the gallbladder, including the hepatoduodenal ligament, making an LC more demanding [267]. Adhesions, operation time, and bile duct damage did not significantly differ between the groups [267]. Others claim that time interval is of no importance. Male gender, bilirubin levels during ERCP, severe adhesions during LC, and pre-LC CRP levels were associated with an adverse outcome for an LC after ERCP.

> Laparoscopic cholecystectomy should be performed 24–48 h after ERCP to shorten the hospitalization, to avoid another hospitalization, and to reduce the possibility of recurrent biliary events in the interval between ERCP and LC [145, 267].

2.2.6.3 Common Bile Duct Exploration

Although postoperative ERCP remains an essential part in managing retained CBD stones, routine use of preoperative ERCP in patients with suspected CBD stones has declined as a result of low yield, increasing the availability of laparoscopic CBD exploration and the risk of complications. Six cases of laparoscopic [134, 239, 267] and 20 cases of open [8, 10, 30, 131, 133] CBD explorations were described. There was no maternal or fetal morbidity or mortality. Multiple studies have demonstrated safe and effective management of CBD stones in pregnancy with ERCP and sphincterotomy with subsequent LC [30, 65, 241, 253, 267]. Therefore, indications for laparoscopic CBD exploration in pregnant patients, following an episode of biliary AP, are yet to be defined. Some recommend 1 mg of glucagon intravenously for sphincter of Oddi relaxation.

Transcystic Approach

In general, laparoscopic clearance of duct calculi by transcystic duct approach is achieved in approximately 80–90% of attempts, which appears to be a viable alternative to post-ERCP [267]. This approach seems valuable when one considers the potential teratogenic effects of radiation exposure when ERCP is performed during the first trimester and the inability to appropriately shield the fetus from radiation during the third trimester [258]. However, such recommendations for laparoscopic management of biliopancreatic disease to include laparoscopic CBD exploration in pregnancy are yet to be precisely defined.

The location of the bile duct stones, size, number, as well as the anatomy should be considered when choosing between a transcystic approach and choledochotomy. Guidelines for a laparoscopic transcystic approach include [267]:

- Small (<0.8 cm) stones in the CBD
- Limited number of CBD stones (≤5)
- Absence of stones in the common hepatic duct
- Cystic duct joining the CBD on its lateral or posterior aspect

Choledochotomy

Choledochotomy is indicated when [267]:

- Transcystic approach fails or is contraindicated
- Biliary lithotripsy needed
- CBD >7 mm

Intraoperative Cholangiography

Since Mirizzi first described intraoperative cholangiography (IOC) in 1934 [267], the technique has developed from static views to dynamic real-time fluoroscopic cholangiography and recently to three-dimensional dynamic cholangiography [267]. In nonpregnant patients dynamic real-time intraoperative fluoroscopic cholangiogram is achieved with the help of mobile C-arm X-ray equipment, using 10–40 ml (200 mg/ml) as contrast medium and 1 ml glucagon intravenously to release any papillary spasm or, in cases of diabetes mellitus, 1–2 ml (20 mg/ml) intravenous butylscopolamine. IOC with LC was described in eight reports [8, 16, 18, 30, 131, 189, 268, 269]. IOC was used frequently, along with cholecystectomy, until the early 1990s. However, recent literature recommends the use of IOC only in the presence of CBD stones and during exploration of CBD [189]. Radiation exposure during cholangiography is estimated to be less than 0.5 rad. Fluoroscopy generally delivers a radiation dose of up to 20 rads/min but varies depending on the X-ray equipment utilized, patient positioning, and patient size. If the IOC is performed, the use of a shield to cover the fetus is recommended in all trimesters [18, 30]. From these reports, it is clear that there was no maternal morbidity or mortality. However, 1 spontaneous abortion was reported [268].

With the advent of ERCP and MRCP, the need for IOC is minimal, although specialized units use it routinely for demonstrating the anatomy of the biliary tree in general population. There have been no reports investigating the safety of IOC during pregnancy. In the absence of clear evidence, potential risks should be discussed with the patient.

2.2.6.4 Therapeutic Delivery

Therapeutic delivery is sometimes performed in metabolic causes of AP such as hypertriglyceridemia, HELLP syndrome, acute fatty liver of pregnancy, etc. (see Sect. 3.7.3) when reversal of estrogen load is the goal of therapy. It is performed only when all other therapeutic modalities are unsuccessful. It is almost never done for biliary AP (see Sect. 3.7.3.2).

2.2.6.5 Puerperium

The lack of initial appreciation for the higher rate of CBD stones in this group led the authors to initially apply selective criteria for cholangiography. In the latter part of the series, routine cholangiography was applied to the postpartum patients and led to the diagnosis of two patients with CBD stones and none of the traditional risk factors. Three patients (8.8%) had missed CBD stones. The rate in total patient series was 0.6% and 0.4%

in the non-postpartum group (unpublished data, Dietrich and Kaplan). The high incidence of CBD stones, often silent, suggests that routine cholangiography should be the norm in the postpartum patient with biliary tract disease.

Intraoperative Ultrasound

Glasgow et al. did not use IOC but described the use of laparoscopic ultrasound in six patients to exclude retained CBD stones [134].

2.2.7 Prognosis

2.2.7.1 Maternal Outcome

Under conservative treatment, the incidence of recurrent biliary AP was 7–70% [210], which may lead to severe consequences [137]. Hernandez et al. described six pregnant women who underwent cholecystectomies for biliary AP, with a mean hospital stay of 7.8 days and no postoperative complications, recurrence of AP, or fetal loss; four pregnant patients with biliary AP were clinically managed, with a 50% recurrence rate and one fetal loss [32].

Therefore, pregnant women during the third trimester and diagnosed as gallstone-induced acute cholangitis or biliary AP should receive ERCP. After single ERCP (with the complete extraction of calculi), the incidence of post-ERCP AP is 6–16% [137, 256, 257]. When only biliary drainage by ERCP is performed in the first phase, without the preoperative use of somatostatin for prevention of AP, the incidence of post-ERCP AP was 2.9% [248].

As for the fetal outcome, maternal outcome after surgical treatment is also excellent. In all six cases of laparoscopic and 20 cases of open CBD exploration described in the literature, there was maternal morbidity or mortality [202].

2.2.7.2 Fetal Outcome

Fetal outcome after ERCP should be divided according to the underlying pathology and whether diagnostic or therapeutic ERCP is performed. The main cause of fetal mortality and morbidity is the underlying disease, not the procedure itself. When ERCP with biliary sphincterotomy for CBD stones is performed, Gupta et al. analyzed 18 pregnant women during all trimesters who underwent therapeutic ERCP [256]. One woman had a PTD. At follow-up after a median of 6 years, all the babies were healthy. According to the data collected from different centers, one AP, two neonatal deaths, and one abortion (3 months following ERCP) occurred in 23 pregnant patients undergoing ERCP [258]. A recent study on 17 patients in the third trimester treated by two-stage ERCP described full-term labor rate of 67% with 2 patients with self-limiting post-ERCP bleeding (12%) and no post-ERCP AP.

Therapeutic ERCP has a low incidence of maternal complications and prolongs gestational weeks and reduces induced labor rate [248]. ERCP for gallstone-induced acute cholangitis in the third trimester resulted in 66.7% of patients delivered at term. The risk of fetal complications related to ERCP has shown to be less than 5% [270]. The remaining patients delivered by elective CS because of self-decision, not fetal distress. A trend toward a higher rate of fetal mortality (8.0% vs. 2.6%) in the conservative group is reported, suggesting the need for earlier LC (and biliary tract clearance when necessary) during pregnancy [202].

Prognosis after CBD surgery during pregnancy is excellent. Six cases of laparoscopic and 20 cases of open CBD exploration were published. There was no fetal morbidity or mortality [202].

2.3 Symptomatic Choledochal Cysts

2.3.1 Historical Perspective

Since first pathological description by Vater 1723 [271] and first clinical description by Douglas in 1852 [272], more than 400 cases have been recorded in the general population. The first symptomatic case of pregnancy was published by Seyffert in 1888 when the onset of jaundice began after childbirth [273]. The first rupture of the choledochal cyst in puerperium after normal vaginal delivery was published by Friend in 1958 [274] and first case or rupture during pregnancy by Saunders and Jackson in 1969 [275].

2.3.2 Incidence

Choledochal cyst is a rare congenital abnormality of the biliary tract. The condition is reported to be common in Japan and Korea and relatively uncommon in Europe and America; one-third of the cases reported in the literature have been from Japan [276]. Incidence varies from 1:100,000–1:150,000 live births [277] to 1:13,000 births in Japan [278]. Usually diagnosed during childhood, choledochal cysts present for the first time during adulthood in 25% of patients. It is four times more common in females [277]. Up to 1944, there were 14 published cases of choledochal cysts during pregnancy and puerperium [279]. Up to 1978, there were approximately 50 cases of *ruptured* choledochal cysts published, in general population, including pregnancy and puerperium [280]. Up to 2007 there were 21 cases diagnosed during pregnancy and significant number during labor and early puerperium [273, 274, 279, 281–310]. Most patients were nulliparous [301]. The Todani I type was present in 82% of cases [301].

2.3.3 Pathophysiology

Choledochal cysts are an uncommon cause of obstructive jaundice, but there is a tendency for them to present in pregnancy [279, 281]. The cyst expansion with pain and jaundice caused by a choledochal cyst in pregnancy may be due to hormonal effect (progesterone-induced stasis, relaxin), compression of the bile duct lumen and cyst by the gravid uterus, and increase in intra-abdominal pressure during pregnancy and labor [284, 301, 303, 307].

2.3.4 Clinical Presentation

Clinical manifestations are nonspecific and variable. In late pregnancy, the symptoms may exacerbate due to hormonal effects and the compression of the CBD by the enlarging uterus [302]. The characteristic Charcot's triad (right upper quadrant abdominal pain, jaundice, and fever) sometimes with right hypochondrial mass occurs mostly in childhood and seldom in adults and is present in one-third of patients in pregnancy [283, 307]. With all anatomic changes during pregnancy, the cyst is not easily detected in pregnant women especially in advanced pregnancy [304]. If silent, it can be unnoticed during pregnancy or found during routine abdominal sonographic screening. Most (75%) patients present with abdominal pain in the upper right quadrant due to enlarged or palpable mass, jaundice (50%), and nausea or vomiting (50%) [301]. Reported complications include cholangitis, AP [282, 304], a cystic rupture with biliary peritonitis [283], and malignancy within choledochal cyst [285]. When the biliary obstruction is present, the symptoms are similar to the symptoms of CBD stones (see Sect. 2.2). Perforation occurs mostly in the late third trimester or during labor [280] when intra-abdominal pressure is at the maximum. Another possibility is the destruction of the cystic wall by inflammation (cholangitis) especially when biliary obstruction is present.

2.3.5 Differential Diagnosis

Due to various possible presentations, the differential diagnosis is different. When choledochal cyst presents as obstructive jaundice in pregnancy, it is usually due to viral hepatitis or intrahepatic cholestasis of pregnancy. Most common etiologies are presented in Table 2.1.

2.3.6 Diagnosis

Pregnancy makes a diagnosis of this disease more difficult because similar symptoms are often encountered during a normal pregnancy. Routine hematological and liver function test are often of limited value. The radiographic study is limited by fetal exposure. Abdominal ultrasonography is commonly used as the initial screening examination in the evaluation of (painful) abdominal mass, acute abdomen, or hepatobiliary conditions. However, difficulties may arise due to distortion of the normal abdominal anatomy and gravid uterus during pregnancy. The cyst may be misdiagnosed as an ovarian tumor or mucocele [309].

ERCP or CT may provide more accurate information, but ionizing radiation should probably be avoided in pregnancy [286]. MRI is suggested as the preferred examination due to the high resolution of the biliary tree without the problems associated with exposing the mother and the fetus to ionizing radiation [310]. MRI can even define the type of choledochal cyst (Figs. 2.9 and 2.10).

2.3.7 Treatment

Although choledochal cysts rarely occur in pregnancy, clinicians need to be aware of the condition, as delayed or inappropriate therapy may be catastrophic for both mother and child. Once the diagnosis is established, patients should be referred to specialized centers where treatment can be carefully planned due to the likelihood of cyst-related complications both in the short- and long-term period. The timing of the operation depends on the type of presentation (elective or emergent presentation), and the type of operation depends on the type of the cyst according to the Todani classification as in nonpregnant patients. The same surgical principles in the postpartum period as during pregnancy are recommended—emergent presentation requires an emergent operation [305]. Otherwise, the patient should be operated electively after the puerperium or even better after the termination of breastfeeding to minimize possible complications of surgery or medication therapy related to the newborn.

Fig. 2.9 MR of the abdomen showing 22 weeks pregnant patient with gallbladder calculi and choledochal cyst (*white arrow*) also filled with calculi. Reproduced with permission from [300]

2.3.7.1 Obstetric Management

The route of delivery in a patient with choledochal cyst is controversial. If untreated, there is the possibility of cyst rupture due to the increased intra-abdominal pressure during labor, and it has been suggested that full-term delivery should be done by CS. If percutaneous external drainage is performed for cyst decompression, then vaginal delivery is not contraindicated [303, 306].

2.3.7.2 Asymptomatic Patients

If presented as an asymptomatic (palpable) mass without other symptoms, the patient should be

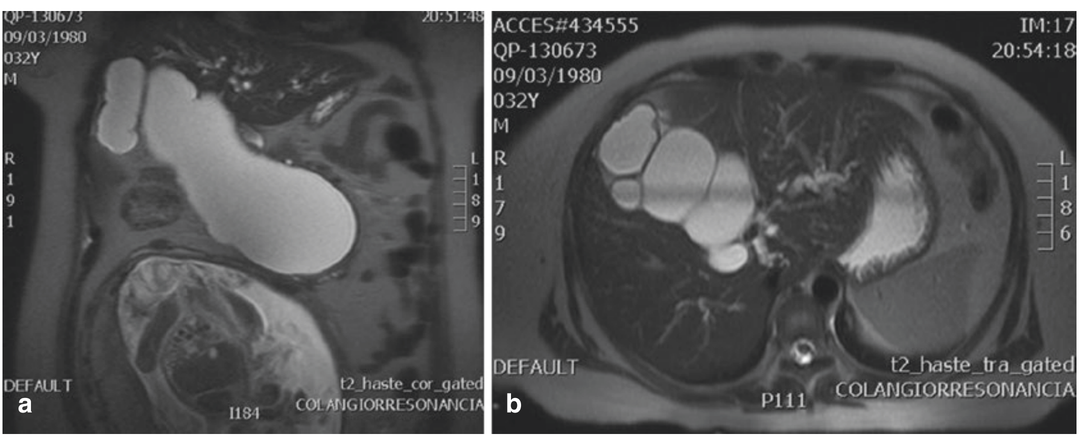

Fig. 2.10 Coronal (**a**) and axial (**b**) view of MR cholangiopancreatography showing large Todani I type choledochal cyst in 22 weeks pregnancy. Reproduced with permission from [311]

checked regularly. There are several treatment strategies. The first option is that definitive treatment is postponed after labor and puerperium to minimize the influences of the operation on the mother and fetus. Second, after elective CS at term, definitive treatment of the choledochal cyst is performed in the same act. The first option sounds more logical and is recommended because during pregnancy, (a) complex surgical procedures result in long recovery and possible complications which affect both mother and fetus, (b) hemostasis may be difficult due to a hyperemic state in pregnancy, and (c) the operative view might be obscured by the gravid uterus. There are no recommendations about timing after CS: (a) some perform definitive surgery 6 weeks after delivery [302, 307] and (b) others, in order to avoid complications during pregnancy and puerperium, delay definitive surgery of the choledochal cyst until the patient's general physiological condition become normal after elective CS [302].

Indications for the semi-urgent surgical intervention of an asymptomatic choledochal cyst in pregnancy include (a) symptomatic cysts, (b) increase in size on serial ultrasound screening, or (c) suspected/confirmed cholangiocarcinoma.

In elective settings recommended surgical technique in pregnant as in nonpregnant women is complete excision of the extrahepatic duct, cholecystectomy, and Roux-en-Y hepaticojejunostomy because the risk of malignant degeneration has been reported to be as high as 30% [312]. In addition, cyst excision minimizes postoperative complications. Sometimes, if the cyst is large, even bilateral Roux-en-Y hepaticojejunostomy could be performed [309]. Complete excision of the extrahepatic bile duct from the hepatic hilum to the pancreaticobiliary duct junction is the most radical solution, in some cases combined with pancreaticoduodenectomy or hepatic resection. These operations are not always possible because of the danger to the structures in the porta hepatis, especially when there are repeated attacks of cholangitis leading to adhesion formation. In such cases, choledochocystoduodenostomy is performed. A side-to-side anastomosis is performed between the most dependent part of the choledochal cyst and the second part of the duodenum. Endoscopic sphincterotomy of type III cysts is the method of choice. Treatment for type IVa cysts (combined extra and intrahepatic biliary dilatation) is still controversial. Total cyst excision including hepatectomy has been recommended in both general [313] and pregnant [286] population. Concerning type V cysts, some recommend hepatic resection for unilobar Caroli's disease [314].

2.3.7.3 Complicated Choledochal Cyst

Acute Cholangitis

The complication in the form of acute cholangitis can occur: a) as the progression of the natural history of the disease and b) it was also described after CS possibly due to kinking of the CBD. Acute cholangitis (with or without biliary obstruction) can be treated first by percutaneous cystic decompression under US, CT, or MRCP guidance. Antibiotics should be administered. After labor and possibly puerperium, definitive excision of the cyst and a hepaticojejunostomy with Roux-en-Y reconstruction are recommended [119, 304]. If the patient is in late pregnancy, elective CS followed by percutaneous decompression after 6 weeks is recommended [302]. There are no recommendations, but some surgeons performed definitive surgery 6 weeks after delivery [302, 307].

However, symptoms from complications such as AP [282, 284] or biliary obstruction [119] require a more urgent approach. Some authors recommend, in order to avoid complications during pregnancy, definitive surgical management of the choledochal cyst should be delayed until the patient's general physiological condition becomes normal after elective [302] or emergent CS [284].

Choledochal Cyst Rupture

Such patients present with acute abdomen, and due to the rarity of the disease and sometimes nonspecific nature before the rupture, it is difficult to reach definitive diagnosis preoperatively. During surgical exploration, the presence of bile-stained intra-abdominal free fluid with a dilated CBD should raise the possibility of a ruptured choledochal cyst [287]. Confirmation can be

Fig. 2.11 Intraoperative picture of choledochal cyst with perforation seen in the anterior wall of the bile duct. Reproduced with permission from [315]

done by intraoperative cholecystography [308] or transcystic cholangiography after cholecystectomy [283]. Sometimes rupture is evident intraoperatively (Fig. 2.11). When the diagnosis is confirmed, the initial step is thorough lavage and insertion of a T-tube. This is followed by a definitive operation which comprises excision of the choledochal cyst with the restoration of biliary-enteric continuity. This is done as an elective operation (after MR cholangiography or postoperative cholangiography [315] as a part of a treatment strategy): (a) in the second trimester [288], when fetal complications are the least common, (b) as part of the CS in the third trimester [285], or (c) in the postpartum period [306, 315].

2.3.8 Prognosis

2.3.8.1 Maternal Outcome

Maternal prognosis is excellent. The largest review of collected cases found 90% of maternal survival [311].

2.3.8.2 Fetal Outcome

The largest review from 2016 with 30 cases could not collect the data for 11 fetal outcomes. From the remaining 19 cases, the mortality was 26.3% [311]. In a review from 2007, 14% of cases with known data ended with the loss of product, 43% in CS, and 43% in vaginal delivery. The abortions occurred in patients with complications – biliary peritonitis, cholangitis, AP, and postoperative sepsis [301].

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3 Acute Pancreatitis

Abstract

Acute pancreatitis (AP) is a rare entity in pregnancy, mainly caused by hyperlipidemia or gallbladder disorders, in which symptoms of cholelithiasis and biliary sludge in many cases precede the symptoms and clinical picture of AP. Diagnosis is based on clinical presentation, laboratory investigations, and modern imaging methods such as abdominal magnetic resonance imaging or magnetic resonance cholangiopancreatography. General management of mild AP in pregnancy is conservative and supportive, while severe AP deserves hospitalization in intensive care unit and endoscopic or surgical interventions. Biliary AP can be resolved with urgent ERCP sphincterotomy followed by laparoscopic cholecystectomy preferably in the second trimester when technical conditions are optimal and risk for the fetus and pregnant woman minimal. Hyperlipidemic AP is treated with lipid-lowering methods, sometimes even with a therapeutic delivery. One of the most common types, biliary AP, is associated with better outcomes than non-biliary causes.

3.1 Historical Perspective

Acute pancreatitis (AP) during pregnancy is extremely rare. German gynecologist Wilhelm Joseph Schmitt (1760–1827) working in Wien reported the first case of pregnancy complicated by hyperlipidemic AP in 1818 [1], in a 30-year-old woman, who died in the fourth month of her eighth pregnancy. William Lawrence (Fig. 3.1) in [2] described the second case also with maternal

Fig. 3.1 Sir William Lawrence (Cirencester, 16 July 1783–London, 5 July 1867), son of a surgeon, helped the founding of the *Lancet* journal, elected to the *Council of the Royal College of Surgeons* in 1828, and became its President in 1846 and again in 1855. He also became *Serjeant Surgeon* (an officer of the Medical Household of the Royal Household of the Sovereign of the United Kingdom). Figure from Wikipedia

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_3

mortality. It is difficult to know whether the AP (macroscopic description without a definitive microscopic diagnosis) started during advanced pregnancy, but that is the most probable situation according to the text from the original article. The pregnant woman was extremely thirsty during advanced pregnancy and postpartum. Was the reason inflammation and sepsis or possible (gestational) diabetes mellitus (GDM) it is not known. Lawrence later collected a series of 53 cases. German author, Marcus, collected 44 cases up to 1930 [3]. Longmade and Edmondson [4] added nine personal cases. In 1952 four additional cases were reported from France [5]. Acute fatty liver of pregnancy (AFLP) and AP were first recognized as a specific clinical entity by Sheehan in 1940. The first report of postpartum AP seems to be by Haidlen in [6], and other early cases were reported by Watts [7] and Deaver [8]. Joske collected personal series of six patients with postpartum AP presentation [9].

3.2 Incidence

Incidence varies more significantly than in general population (England, Denmark, and the United States: 4.8–24.2/100,000 [10]), ranging 1/1000–1/12,000 pregnancies, and rarely progresses to the necrotizing form [11–17]. It is more common in East Asian countries, including China, where AP in pregnancy accounts for 4.25% of all (unknown whether only women or both sexes included) AP [18] or 1/441 pregnancies [19].

Accurate assessment of disease incidence in pregnancy is difficult due to several factors. During normal pregnancy, patients expect some degree of abdominal pain; therefore, the mild disease may be underreported. Also, there is an issue with the definition of AP in pregnancy. Some included a period of 10 months prior to parturition which ends up 10 months postpartum [20], while standard definition of the postpartum period is 6 weeks [3]. In addition, some causes are attributed to biliary stones without definitive confirmation. Biliary sludge and gallstones are present in 10% of people in Western countries. The incidence rises in pregnancy, and it is questionable that gallbladder stones or sludge caused AP in some patients without definitive diagnostic elimination of all other causes. In some studies, nearly 70% of cases are secondary to biliary stones or sludge, followed by hyperlipidemia and alcohol abuse in approximately 20% of cases, respectively [11, 21, 22]. Therefore, the discrepancy in incidence is due to [23]:

- The rarity of disease
- Postpartum period up to 10 months
- Different decades and countries
- Underestimation due to underreporting
- Small number of cases in studies
- Multiple possible causes not definitively excluded

3.2.1 Age, Trimester, and Race

More and more women become pregnant in more advanced age, and it is known that the incidence of AP in general population increases with age [24]. Mean age in two largest studies up to 1973 was 24.2 and 27 years, respectively [4]. Up to 1951, data showed that primipara suffered from AP more often than the multipara. The primipara is, even more, subject to the disease if she has gallstones [4]. Current studies show that AP is more frequent in multiparous patients, in 64–75% [11, 25, 26].

The Hispanic population has a higher incidence (0.1%) due to higher risk for gallstone disease [27]. Alcohol-induced AP is rare in countries (especially the Middle East), where alcohol consumption is forbidden.

AP appears to be more prevalent with advanced gestational stage, occurring most commonly in the third trimester [21, 22, 28, 29]. Trimester distribution depends on the population studied and varies: 19–28% in the first, 21–33% in the second, 43–78% in the third, and 2–38% in the puerperium [11, 23, 25–27, 30]. The proportion of severe AP also fits the rule that frequency increases with gestational age (1st, 2nd, 3rd at 0%, 11.1%, 88.9%, respectively) with a much larger span [30]. The trimester distribution is consistent with (1) a potential lithogenic effect of

estrogen during pregnancy [11, 23]; (2) a physiological type of insulin resistance in the second and third trimesters of pregnancy [31]; (3) a progressive physiologic increase in both serum cholesterol and triglyceride concentrations, with peak levels reached at term, in response to elevated estrogen levels; (4) possible compression effect of uterus on biliary tree, pancreatic vessels, and pancreas itself; and (5) significant rise in intra-abdominal pressure due to prolonged second stage of labor [32].

3.2.2 Hyperlipidemia/Dyslipidemia

Chylomicronemia occurs when plasma triglyceride levels exceed 1000 mg/dL. The *chylomicronemia syndrome* is defined when chylomicronemia is accompanied by one or more of the following:

- Eruptive xanthoma (see Sect. 3.4): small yellowish papules, frequently with an erythematous base, appearing predominantly on the buttocks and elbows caused by deposition of large amounts of chylomicron triglycerides in cutaneous histiocytes.
- Lipemia retinalis (see Sect. 3.4): the retina has a salmon-colored, creamy appearance, and the retinal vessels are white.
- Abdominal findings: abdominal pain, acute pancreatitis, and/or hepatosplenomegaly.

The association of hyperlipidemia with AP during pregnancy was first reported in 1818 and was the first published case of AP during pregnancy [1]. By 1970 a total of only 101 reports had been published. Approximately 15 cases have been described in the period 1956–1996 [33]. Previously, 1.7–6% of cases of AP in pregnancy were attributed to hyperlipidemia [34, 35]. Currently, AP secondary to hyperlipidemia/dyslipidemia has an estimated incidence of 1/25,000 births [36], or 10–56% of all cases [29, 37, 38], which is much higher than the incidence of 1–7% in nonpregnant population [39, 40].

There are several reasons for failure to consider and investigate chylomicronemia as a cause of AP which may lead to an underestimation of its incidence. First, some cases are declared idiopathic due to lack of lipid profile testing. This confirms the importance of pre-screening for triglyceride (TG) levels before initiation of estrogen-related medical treatment such as IVF [41]. Second, determining the exact etiology of AP may be complicated by the role of ethanol in precipitating severe hypertriglyceridemia. The same problem with defining etiology is present in hypothyroid patients or patients with DM. Third, within 24–48 h of the onset of AP, in the majority of patients, TG levels fall rapidly as a result of fasting status, when the supply of chylomicrons from the intestinal absorption to the blood is cut off. Also, once therapy with hypocaloric intravenous fluids is started, there is a decrease in the secretion of very low-density lipoproteins (VLDL) from the liver, which further reduces the TG pool and causes a decrease in the levels [42]. Therefore, if lipid profile is not checked during admission, it could be a false negative. Additionally, the clinicians should not confuse the universal mild to moderate hyperlipidemia secondary to AP with the marked hypertriglyceridemia (HTG) that causes AP [43]. Whether the elevated TG is an epiphenomenon of the AP or the actual cause of the inflammation can be difficult to differentiate. In general population, the serum in patients with AP may be lactescent in 4–20%, and lipid levels increase above the normal in up to 50% of patients with AP of any cause [44–48]. Gunduz et al. found an equal distribution of HTG-induced AP through trimesters [29]. Approximately one-third of the women developing HTG-induced AP during pregnancy were nulliparous [11, 49].

3.2.3 Alcohol Abuse

Idiopathic AP in pregnancy is considered to be alcohol-induced in 12-3-16.5 [23, 50]. Alcohol-induced AP was more prevalent in the study by Eddy et al. (17.8% overall; 12.3% of 89 AP cases vs. ≤7% in other studies) [21, 51, 52], due to the inclusion of chronic pancreatitis and also due to inclusion of Midwestern states with a high prevalence of alcohol use [53]. In one Turkish study, there was no single case of alcohol-induced AP, probably as a result of cultural difference

[25]. The onset of alcohol-induced AP in general population usually occurs in the fourth decade, and the average alcohol consumption in patients who develop AP is of the order of 150 g/day for a period of 10–15 years prior to the initial presentation. Alcohol-induced AP is more commonly diagnosed during pregnancy probably because pregnant patients seek medical attention more commonly than female drinkers in general population. Again, one must be cautious with the accusation of alcohol use as a cause to its interrelation with hyperlipidemia.

3.2.3.1 Pancreatic Pseudocysts

The overwhelming majority of pregnant patients with pancreatic pseudocysts are nulliparous (84%), and the majority (61%) presents in the third trimester. While some claim that in both pregnant and nonpregnant patients, pancreatic pseudocysts are most frequently associated with alcohol-induced AP, current data show that hyperlipidemia is the most common cause (Table 3.6). A significant past medical history of alcohol misuse, AP, or both was elucidated in 38% [54]. Although 69% had no identifiable past medical history, approximately a third had an undiagnosed predisposing factor – either familial hyperlipidemia or gallstones [54].

> Non-gallstone AP in pregnancy has been shown to be significantly more prone to pseudocyst formation [11, 23, 33, 55–58].

3.2.4 Primary Hyperparathyroidism

In general population, PHPT is common, with its greatest frequency in postmenopausal women, in whom it reaches a prevalence of 2–3% [59]. The incidence in women of childbearing age (less than 40 years) is approximately 8/100,000 per year [60]. Around 0.5–1.4% of all PHPT occur during pregnancy [61–63]. The most frequent cause of PHPT in the general population is a single parathyroid adenoma (85%), followed by parathyroid hyperplasia (15–20%) and, very rarely (less than 1%), by carcinoma [64, 65]. The occurrence of PHPT during pregnancy was described by Hunter and Turnbull in [66]. More than 100 cases reported in the English literature between 1931 and 1990 were published [60] and less than 200 till 2015 during pregnancy and postpartum [67–72]. Parathyroid adenomas, as in nonpregnant population, are the most common cause of PHPT during pregnancy (81.2%) [73]. Relative paucity of data may be explained by at least three different causes: (1) the average age of the initial manifestation of this disorder is higher than that of women of childbearing age [59, 64, 65], (2) about 80% of nonpregnant individuals with PHPT are characterized by an asymptomatic course of this disease [67], and (3) some symptoms of PHPT may be misinterpreted as a simple consequence of pregnancy or other gestation-related disorders, while physiological changes during gestation may mask some abnormalities typical to PHPT [71, 74].

There is a 28-fold increased risk of AP in PHPT patients compared to the general population [75]. Whereas some series have suggested an association between PHPT and AP, community-based studies showed no increase in the incidence of AP among patients with PHPT as compared with matched controls [70, 76]. PHPT is a rare etiology of hypercalcemic-induced AP, causing 0.4–2% of cases in the general population and significantly higher, 7–13% of cases during pregnancy [25, 61, 67–70, 77]. Others found the wider incidence of PHPT-induced AP in general population of 1–12% [70, 78–80].

The simultaneous occurrence of PHPT and AP in pregnancy has only been reported 13 times up to 1998 [68, 81–89]. There were no cases during the first trimester, and more than 90% of patients had thyroid adenoma (89%) and only one thyroid carcinoma. There is an increased incidence of cholelithiasis in general population with PHPT [90]; therefore, the question is what is the real cause of AP during pregnancy in some of these cases.

3.2.5 Preeclampsia/Eclampsia

Hojo et al. reviewed a total of 15 cases in the literature of AP thought to be associated with preeclampsia between 1956 and 2007 [91].

3.2.6 Pancreatic Neoplasms

Pancreatic neoplasms, both benign and malignant, are uncommon during pregnancy. The most common are cystic pancreatic lesions with 13 published cases diagnosed during pregnancy [92–96]. The first report was in 1968 by Smithers et al. [93]. In general population pancreatic mucinous cystic neoplasms occur almost exclusively in females. There have been only 11 reported cases of pancreatic adenocarcinoma [97] and 3 of pancreatic neuroendocrine tumors. Pancreatic cancer manifested as AP in only one case [97] in a patient with pancreatic adenocarcinoma.

3.2.7 Acute Fatty Liver of Pregnancy

AFLP occurs in 1/7000–1/20,000 pregnancies (see Chap. 2), while others estimate at least two times higher incidence. The association of AFLP and AP in pregnancy exists, but in the last 45 years, less than 20 cases have been reported [12, 98–100]. AFLP is the disease of the third trimester when the most cases of AP are diagnosed. Currently, there is only one published case of chronic pancreatitis after AFLP in a patient with gestational DM [101].

Table 3.1 Causes of acute pancreatitis

Alcohol or methanol abuse (>100 g/day for >3–5 years)
Autoimmune diseases
Choledochal cyst
Cystic fibrosis
Gallstones
Hereditary (familial) pancreatitis (including a mutation of the cationic trypsinogen gene)
Hyperlipidemia or hypertriglyceridemia (1000 mg/dL)
Hypercalcemia/hyperparathyroidism
Infection (Coxsackie B virus, cytomegalovirus, mumps)
Ischemia from hypotension or atheroembolism
Medications (ACE inhibitors, asparaginase, azathioprine, oral estrogens, antibiotics, 2′,3′-dideoxyinosine, furosemide, 6-mercaptourine, pentamidine, sulfa drugs, valproate, thiazide diuretic, corticosteroids)
Neoplasm
Pancreatic or periampullary cancer
Pancreas divisum
Peptic ulcers
Preeclampsia/eclampsia
Post-ERCP
Postoperative inflammation
Post-renal transplant
Sphincter of Oddi stenosis
Blunt or penetrating trauma
Surgery (ischemia/perfusion/mechanical)
Tropical pancreatitis
Vasculitis
Viral infections
Idiopathic

3.3 Etiopathogenesis

3.3.1 Introduction

Mnemonics for etiology of AP is “IT GET SMASHED”: idiopathic, trauma, gallstones, ethanol, tumor, steroids, mumps, autoimmune, scorpion venom, hyperlipidemia, ERCP, drugs. Comprehensive list of causes in general population that apply also to pregnant population (with somewhat different incidences) is shown in Table 3.1. For AP associated with pregnancy, a time limit of 6 weeks postpartum is defined [3].

Despite several cases published previously, the possible association between AP and pregnancy was first suggested by Mondière in [102]. In 1955, Ross suggested a rise in intra-abdominal pressure such as undue prolonged second stage of labor as etiology of AP in pregnancy [32]. Elevation of intra-abdominal pressure leading to the high pancreatic ductal pressure [103] and increased tonus of the Oddi’s sphincter may be other possible mechanisms to induce or promote AP of any cause (see Sect. 3.3.6).

The trigger events or precipitating factors for AP in 60% of pregnant women are associated with excess high-fat/high-protein diet. The favored explanation may be that large amounts of bile/trypsin release can overwhelm the defense mechanism and activate other enzymes, resulting in local and systemic complications that are commonly seen in the course of the disease [104].

An additional pathophysiologic phenomenon in pregnancy is GDM. Severe diabetic ketoacidosis and hyperglycemia with associated dehydration are known risk factors of AP in general population. It

could be a trigger for AP in pregnancy. Most commonly DM is a part of a metabolic syndrome (see Sect. 3.3.5). It is still not clear, whether the pathogenesis of AP is one entity or whether it consists of a group of distinct pathogenetic mechanisms. Idiopathic AP is the cause in 10% of cases [22], with declining incidence, as the knowledge of genetic causes, exogenous etiologies, and more precise diagnostic imaging accumulates.

3.3.2 Biliary

During pregnancy, gallstones and biliary sludge were accused as the most common causes of AP, causing pancreatic duct/ampulla of Vater obstruction with pancreatic hyperstimulation that increases pancreatic duct pressure, trypsin reflux, and activation of trypsin in the pancreatic acinar cells. This leads to enzyme activation within the pancreas and causes autodigestion of the gland, followed by local inflammation (Fig. 3.2). Pregnancy does not primarily predispose the pregnant woman to AP, but it does increase the risk of cholelithiasis and biliary sludge formation (see Chap. 2) [11]. Biliary AP occurs in relatively older age (28.2 years) as compared to non-biliary AP (24.4 years). In both groups, pregnant women were usually multiparous and AP mostly presented in the third trimester [22]. One must be cautious with these data because due to differences in the distribution of etiologies of AP throughout the world (see Sect. 3.2).

3.3.3 Primary Hyperparathyroidism

3.3.3.1 Calcium-PTH Metabolism in Pregnancy

Pregnancy and lactation are characterized by important alterations in calcium-PTH homeostasis/dynamics, being a consequence of pregnancy-induced changes in the synthesis, metabolism, and excretion of calcium and calcitropic hormones [71, 105]. Early reports described a *physiological hyperparathyroidism of pregnancy* with an increase in serum PTH levels beginning in the second trimester [106]. However, the development of more accurate and specific methods has discredited this by showing a reduction, rather than an elevation, of intact PTH levels [107]. In fact, mean serum PTH levels in nonpregnant women prove to be 72% higher than in pregnant women [108]. These changes in PTH during pregnancy may be a response to altered calcium metabolism. Intravascular fluid expansion and hypoalbuminemia (albumin falls by 20%) make less protein available to bind calcium, thus lowering total (maternal serum calcium falls by about 10%) but not ionized calcium [108]. Approximately 50% of serum calcium is protein bound, mostly to albumin; 10% is complexed to anions, and 40% circulates free as ionized calcium. In addition, an increase in urinary excretion of calcium occurs due to increased glomerular filtration rate, and maternal calcium in the blood is actively transported across the placenta to the growing fetus [109]. Hypercalcemia is defined as (corrected) total serum calcium above the standard laboratory reference range (2.2–2.6 mmol/L). In pregnancy, the reference range is marginally lower depending on the trimester (Table 3.2).

The latter imposes an increased calcium requirement that is partly fulfilled by mobilization of calcium from the maternal skeleton. Together, these effects have a tendency to lower maternal calcium levels [110]. During pregnancy, the placenta actively transports calcium ions to the fetus but does not allow transfer of PTH [111]. Fetal blood, as measured by cordocentesis, has a 0.5–1 mEq/L higher concentration of calcium. Elevated concentrations are required secondary to an increased demand by the fetus for adequate bone mineralization. Increased demand is met through active transport by the placenta via a maternal fetal gradient of 1:1.4 [112, 113]. The parathyroid glands, which produce PTH, are stimulated by hypocalcemia and suppressed by high concentrations of calcium, magnesium, and $1,25(OH)_2D_3$ and also by hypomagnesemia. PTH influences calcium metabolism, not only by directly reabsorbing bone but also by stimulating $1,25(OH)_2D_3$ formation. Maternal serum PTH levels, when measured by a sensitive assay that accurately measures the levels of intact PTH, are slightly decreased in the first half of pregnancy (20% of the mean nonpregnant values) and

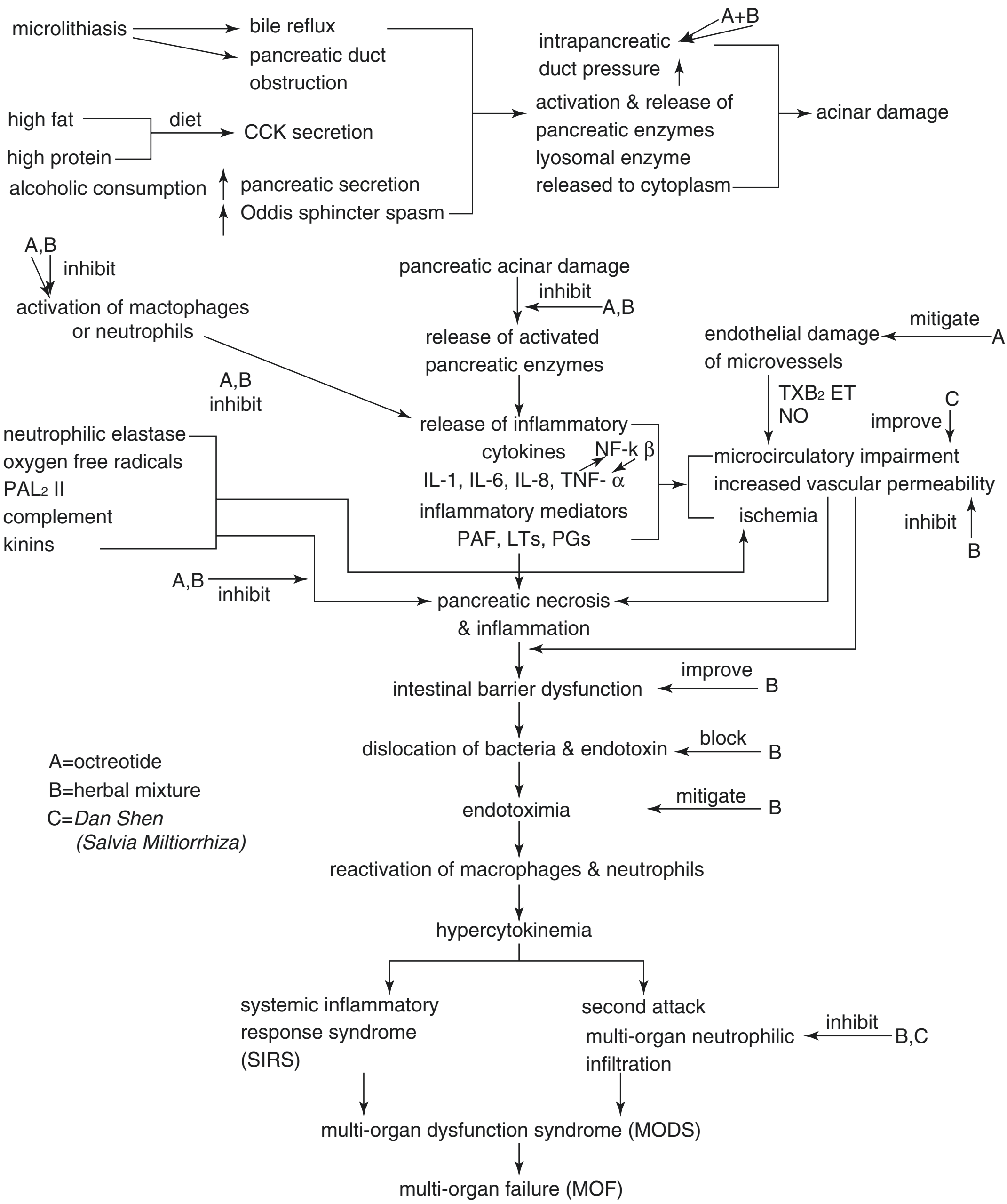

Fig. 3.2 Schematic representation of step-by-step pathogenesis of (biliary) acute pancreatitis with the possible action of medications. *CCK* cholecystokinin, *NO* nitric oxide, *TXB2* thromboxane B2, *TNF-α* tumor necrosis factor α, *PAF* platelet activating factor, *PG* prostaglandin

Table 3.2 Corrected serum calcium in pregnancy

Normal	First trimester	Second trimester	Third trimester
2.20–2.60 mmol/L	2.25–2.57 mmol/L	2.30–2.50 mmol/L	2.30–2.59 mmol/L

return to normal by mid-gestation [71]. Blood levels of 1,25(OH)$_2$D$_3$ (calcitriol) increase early in gestation as a result of stimulation of renal 1-α-hydroxylase activity by estrogen, placental lactogen, and PTH, as well as the synthesis of cal-

citriol by the placenta [114]. Both free and total 1,25(OH)$_2$D$_3$ are increased in pregnancy, the total because of an increase in vitamin D-binding protein (Fig. 3.3).

Elevated calcium levels ultimately result in fetal PTH suppression. Maternal PHPT can, therefore, result in fetal hypercalcemia which substantially increases the risk of spontaneous abortion [116]. Maternal PHPT results in an even further suppression of fetal PTH, which accounts for the hypocalcemic effects on the fetus at birth [113]. However, they are more than offset by a large increase in intestinal calcium absorption that occurs during pregnancy [117]. Hormonal changes during pregnancy may also be responsible for an increase in the production or activity of the enzyme 1-α-hydroxylase in the kidney [118], which in turn may account for the observed differences between pregnant and nonpregnant women, including the elevation of 1,25-dihydroxyvitamin D [107], the slight increase in serum calcium levels [119], and the reduction in PTH levels [108]. Fetal 1,25-dihydroxyvitamin D, synthesized in fetal kidney and placenta, acts as the major stimulus and regulator of calcium transfer across the placenta. It increases maternal gastrointestinal absorption of calcium by 150–400 mg/day; additionally, maternal urinary excretion is also increased from 90 to 300 mg/day. Major fetal calcium demands of approximately 25–30 g are required in the third trimester for skeletal tissue mineralization. This requires an active transport of calcium across the placenta, and the fetal serum calcium remains higher than maternal blood. Conversely, after delivery, when the maternal transplacental supply of calcium ceases, neonatal hypocalcemia becomes the major problem. This may occur because the neonate is unable to mobilize calcium stores adequately as a result of prolonged parathyroid gland suppression.

The initiation and growth of kidney calculi may be attributed to overlapping of both increased

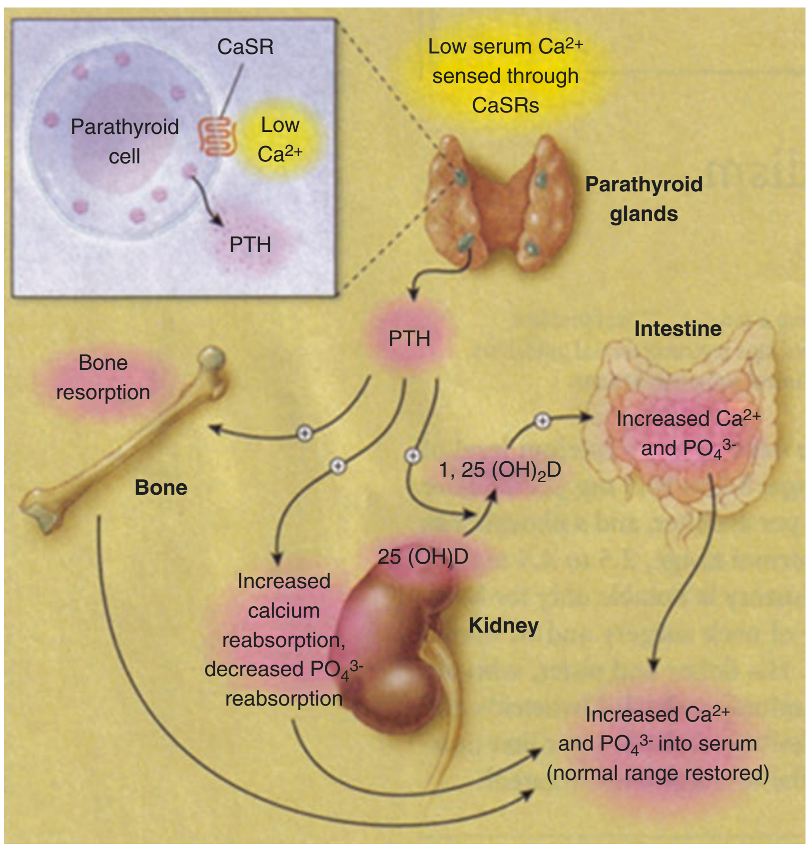

Fig. 3.3 Control of mineral metabolism by parathyroid hormone; serum ionized calcium (Ca^{2+}), parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25[OH]$_2$D), calcium-sensing receptors (CaSRs), phosphorus (PO_4^{3-}), 25-hydroxyvitamin D (25[OH]D). Reproduced with permission from [115]

calcium load, secondary to enhanced PTH synthesis and release, and a pregnancy-induced increase in urine calcium excretion.

3.3.3.2 Calcium-Induced Acute Pancreatitis

After eliminating all other causes, mean plasma calcium level seems to be the only predictive factor for AP development [75, 78, 120]. In addition, genetic mutations constitute a greater risk factor for AP than serum calcium [80].

> The pathophysiologic mechanism that leads to AP seems more related to hypercalcemia than to PHPT. Hypercalcemia from any cause can lead to AP.

Calcium ions cause calculus deposition within the pancreatic ductules, with consequent obstruction and inflammation [121]. Moreover, calcium can trigger the AP cascade by promoting conversion of trypsinogen to trypsin [122]. The interrelation between AP and parathyroid function can be summarized as follows: (1) AP results in a tendency to hypocalcemia and secondary hyperparathyroidism [123, 124]. Compensation need is correlated to AP severity as shown by PTH level [125]; (2) severe and/or complicated AP can lead to overt hypocalcemia through relative deficiency in PTH secretion [124], because exogenous administration of PTH normalizes calcium level [126]; (3) in severe AP, resistance to PTH action in bones and kidneys may occur because of fluid sequestration and reduction in efficient arterial blood volume [123]; and (4) once the diagnosis of PHPT-induced AP is established, parathyroidectomy is mandatory preventing its recurrence [61, 78].

The fact that AP is present in three of four pregnancies complicated by PHPT, while never occurred before and between pregnancies, strongly supports that gestation makes PHPT patients particularly prone to AP. It is assumed that AP occurs more frequently in primiparous than multiparous women and occurs mainly in the first and third trimester [72, 73]. PHPT can result in calcifications in the pancreatic ducts thereby blocking secretions, which then damage the pancreatic tissues and result in AP [81]. Usually, this is present with higher calcium levels compared to PHPT without AP [81]. Although the absolute calcium level is an important predictor, it may attenuate during the pregnancy, and individual predisposing factors may be important in the manifestation of pancreatic inflammation [89].

Although most young women with hypercalcemia have PHPT, other unusual causes should be ruled out (Table 3.3).

Table 3.3 Causes of hypercalcemia during pregnancy other than primary hyperparathyroidism

Familial hypocalciuric hypercalcemia
Postpartum hypercalcemia in hypoparathyroidism
PTHrP-induced hypercalcemia
Malignancy
Thyrotoxicosis
Adrenal insufficiency
Vitamin D overdose
Vitamin A overdose
Thiazide diuretics
Lithium
Granulomatous disease
Sarcoidosis
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Milk-alkali syndrome
Acute/chronic renal failure
Total parenteral nutrition

3.3.4 Acute Fatty Liver of Pregnancy

It appears that 39% of AFLP cases are secondary to a urinary or respiratory infection [127]. It is more common in women with multiple pregnancies and, possibly, in underweight women. In all cases, multiple organs are involved. The pathophysiology of the disease is obscure. The deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in the fetus may be implicated in the pathogenesis [128]. A fetus with this enzyme deficiency accumulates long-chain

fatty acids that have not undergone oxidation. These fatty acids enter the mother's serum and are hepatotoxic. Furthermore, the placenta itself may produce excess fatty acids and may further elevate the level of maternal free fatty acids (FFAs). Mothers who are heterozygous for LCHAD deficiency also have a greater risk of developing AFLP [128]. The long-chain LCHAD deficiency in the mitochondria determines long- and medium-chain fatty acid accumulation into the cell. This defective enzyme is determined by a gene mutation (E47Q) [129] with an incidence of 1:150–1:200 in population. Other hypotheses favor above-normal (for pregnancy) level of estrogens potentiating the effects of an otherwise tolerable hormonal insult to the mitochondria in the third trimester.

Data show that 34% of patients in general population who died from AP had macroscopic liver steatosis [130]. Therefore, hepatic problems could be the origin of pancreatic disease by observing extraordinarily high concentrations of lipoperoxide in the bile of patients with pancreatic disease [131]. Pancreatic toxicity is probably due to FFAs, similar as in HTG-induced AP (see Sect. 3.3.5), and the hypothesis is that the accumulation of long-chain metabolites of 3-hydroxyacyl is toxic to the liver and the pancreatic tissue [98].

3.3.5 Hyperlipidemia/Dyslipidemia

3.3.5.1 Hereditary/Physiologic

Maternal metabolism must satisfy the demands of the developing fetus in addition to energy requirements of the mother. Early pregnancy is an anabolic phase, characterized by increased hepatic production of triglycerides and enhanced removal of triglycerides from circulation, resulting in an increased deposition of fat in maternal adipose tissue. In contrast, late pregnancy is a catabolic phase with the release of FFAs from adipocytes enhanced by both relative insulin resistance and stimulation of hormone-sensitive lipase by placental hormones. These metabolic changes allow the metabolism of gravid female to store energy in early pregnancy to meet the energy requirements of late gestation.

Maternal hypertriglyceridemia and hypercholesterolemia (*maternal physiologic hyperlipidemia*) contribute to fetal growth and development and serve as an energy depot for maternal dietary TGs and fatty acids [132], sparing the glucose for the fetus. Serum lipid and lipoprotein concentrations during pregnancy are modulated by complex interactions between genetic and metabolic factors. The *estrogen:progesterone ratio* is important in the balance of the metabolism of lipoprotein during pregnancy. Progesterone opposes the action of estrogen on lipoprotein metabolism [133]. During the first trimester, the ratio is low indicating a predominantly progesterone-mediated effect on lipid metabolism with lipoprotein levels lower than prepregnancy baseline levels. The total cholesterol and TG increase during the second and third trimester due to increase in estrogen levels and its influence on the increase in lipoprotein levels (Fig. 3.4).

Plasma TG levels increase two- to three-fold [135], rarely exceeding 3.3 mmol/L (300 mg/dL). This physiological increase during pregnancy is not sufficient to cause AP. Preexisting genetic abnormalities in the lipid metabolism may be exacerbated during pregnancy and can cause gestational hyperlipidemic AP. The elevation in TG levels is greater than that of cholesterol (an increase of 50%) and phospholipids (Fig. 3.4).

Lipoprotein lipase (LPL) is a key enzyme for the hydrolysis of TG from chylomicrons and VLDL particles of blood plasma. LPL activity

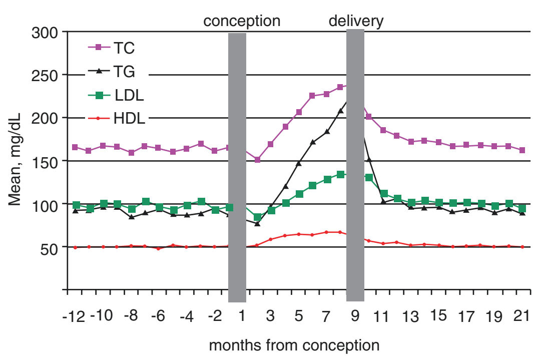

Fig. 3.4 Lipid level variations during normal pregnancy are characterized by an initial decrease from the prepregnancy baseline levels during first trimester followed by the gradual increase and peaking before the delivery. Reproduced with permission from [134]

can be modulated by exogenous and endogenous mechanisms. Exogenous mechanisms include combination of the following:

1. A human placental lactogen-related increase (secreted by trophoblast cells) and prolactin level increase inhibit adipose tissue LPL activity resulting in a rise in the concentration of plasma TG and FFA level in serum [136].
2. Hepatic synthesis of VLDL results in increased production of TG-rich lipoproteins [137].
3. Up- or downregulation by insulin, estrogen, and medications [138, 139].

During pregnancy fasting, plasma TG levels increase predominantly through increased liver synthesis of TG and VLDL in response to elevated estrogen levels [140]. The presence of lipoprotein receptors in the placenta together with LPL and intracellular lipase activities allows the release of FFAs to the fetus [135]. Endogenous mechanisms consist of the LPL gene mutations. More than 30 mutations have been identified in LPL gene in women with gestational AP [141, 142]. Several mutations in the LPL gene underlying severe hyperlipidemia in pregnancy were detected, the first in 1994 [141].

Mutations of the LPL gene (Fig. 3.5) may result in partial or more rarely complete LPL deficiency. Complete deficiency usually but not invariably presents in childhood with hyperchylomicronemia, eruptive xanthomatosis, and recurrent AP. It could be responsible for a tenfold increase in plasma TG levels [142]. The assumption is that the rarity of the syndrome of hyperlipidemia and AP in pregnancy in patients with this specific genetic defect may be due to the presence of an undetected additional mutation in affected patients [143].

Additionally, the clearance of VLDL and chylomicrons decreases due to a reduction of LPL at the capillary endothelium [138, 144]. This appears to be due to a decrease in LPL synthesis in adipose tissue and possibly skeletal muscle, through the downregulation of LPL gene expression by estrogen [138].

Compared to hypercholesterolemia and mixed hyperlipidemia, HTG increases risks of AP for hyperlipidemic pregnant women [145]. The precise mechanisms for the pathogenesis of HTG-induced AP are not established. HTG is five times more common in pregnant women with AP (38%) compared to pregnant women without AP (9%) [146]. Hydrolysis of excessive TG-rich lipoproteins by high levels of pancreatic lipase releases very high concentrations of FFAs which exceed the binding capacity of plasma albumin, thus resulting in self-aggregating FFA micellar structures with detergent properties

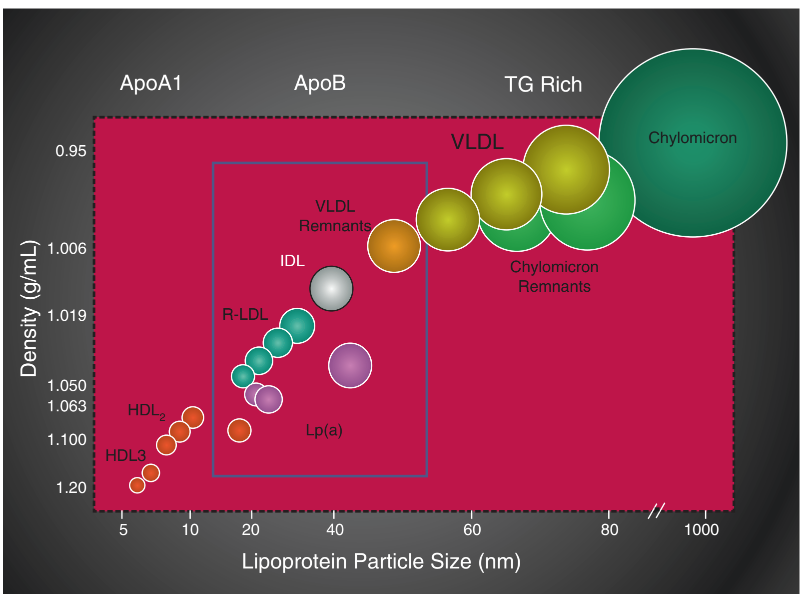

Fig. 3.5 Lipoprotein size-density relationship. Lipid subclasses are present in a continuum of size and density, with an especially large gradient for the TG-rich lipoproteins IDL, VLDL, and chylomicrons. Figure courtesy of Atherotech Labs, Inc., Birmingham, AL

[147]. The elevation in circulating FFAs impairs endothelium-dependent vasodilatation [148], and the decreased endothelial function may be dependent on enhanced oxidative stress [149]. Inflammatory effects of TG-rich lipoproteins are confirmed as increased expression of leukocyte adhesion molecules and monocyte adherence on endothelial cells in response to the inflammatory cytokine tumor necrosis factor-α (TNF-α) [150]. It is possible that estrogen, aside from producing an alteration in plasma TG concentrations, has toxic effects on the pancreas itself. Pancreatic acinar cells have significant amounts of an estradiol-binding protein [151]. Estrogen increases LDL receptors [152], in some situations, and conceivably could promote lipid uptake into acinar cells. Sufficient excess lipid uptake leads to lipotoxicity and cellular apoptosis, a process that is best characterized in muscle cells [153]. Direct effects of estrogens on pancreatic function are supported by the observation that pancreatic amylase release in the rat is stimulated by estrogen [154]. On the other hand, it could be seen that an elevation in estrogen may increase synthesis of TG and depresses plasma postheparin lipolytic activities (PHLA) lowering the removal efficiency of TG during pregnancy. Actually, the production rates of TG and total cholesterol at the end of pregnancy are markedly increased to 140% and 50%, respectively, as compared to that of the nonpregnant period [155]. Additionally, TGs universally increase during an episode of AP. Whether the elevated TGs are an epiphenomenon of the AP or the actual cause of the inflammation can be difficult to differentiate. Mild to moderate elevations of TGs are seen in up to 50% of all-cause AP and are generally regarded an epiphenomenon rather than a cause. However, the increase caused by AP alone is transient, peaking at 72 h and declining to near normal values in 2 weeks [48].

The FFA micelles injure the vascular endothelium and acinar cells of the pancreas, producing a self-perpetuating ischemic/acidic environment. In this acidic environment, FFAs activate trypsinogen and trigger acute edematous and necrotizing AP. Another theory favors ischemia secondary to plasma hyperviscosity due to severe chylomicronemia [156]. However, these two theories are not mutually exclusive (Fig. 3.6). In addition, physical damage by cholesterol crystals might cause microvascular endothelial cell disruption [147].

The development of marked HTG, specifically in pregnancy, in the absence of factors such as DM, drug, or alcohol intake, raises the possibility of partial defects in TG metabolism.

> HTG-induced AP occurs when TG levels are over 1000 mg/dL, while recently it is claimed that the majority of AP cases occur when levels exceed 3000 mg/dL [158].

Patients presenting with severe HTG should be evaluated for a genetic disorder in lipid metabolism. According to Fredrickson classification of dyslipidemias, types I, IV, and V are associated with severe HTG and predispose for AP [159]. Types I and V can present with AP without an exacerbating factor, whereas type IV usually requires secondary precipitating factors (e.g., poorly controlled DM, alcohol use, estrogen, and pregnancy or medications that can increase or raise TG levels) [43]. Type I (familial chylomicronemia) often presents in infancy and is caused by an autosomal recessive trait resulting in LPL or apo C-II deficiency. Type IV (familial HTG or familial combined hyperlipidemia) is autosomal dominant and presents in adulthood.

In addition to HTG-induced AP, hyperlipidemia is an attendant risk of cholesterol gallstone formation and intrahepatic cholestasis of pregnancy [160].

3.3.5.2 Acquired

Estrogen Therapy

Estrogen therapy in DM may lead to an extreme HTG, particularly in an uncontrolled glycemic state, and then possibly induce AP [39, 161, 162]. In type I DM, the absence of insulin reduces the ability of LPL to reduce TG into FFA, resulting in elevated TG levels [163]. In type II DM, insulin resistance leads to enhanced production and reduced clearance of TG [164].

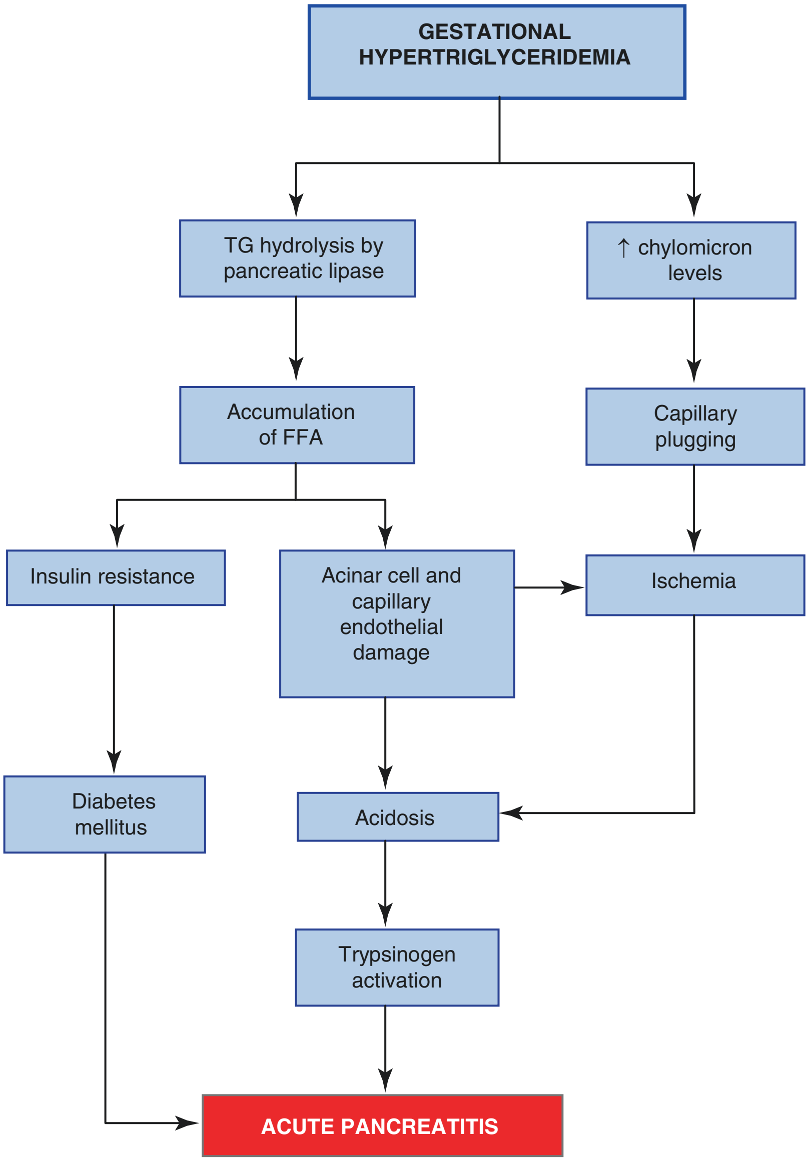

Fig. 3.6 Pathophysiology of HTG-induced acute pancreatitis. *TG* triglyceride, *FFA* free fatty acid. Reproduced with permission and modified from [157]

The role of alcohol in HTG is unclear but may be attributed to alcohol competing with FFAs for oxidation, leaving more FFAs available for TG synthesis [43]. Some authors claim that alcohol alone does not cause HTG, but more likely exacerbates an underlying genetic hyperlipidemia [161].

Accordingly, hormone therapy in women is not recommended when TG is >500 mg/dL due to heightened risk of HTG AP [165]. Exogenous estrogens (especially in high levels during assisted reproduction) elevate TGs by increasing the production of TG-carrying VLDLs by the liver and reducing the levels of LPL and hepatic lipase, thus reducing TG clearance while also elevating TGs by augmentation of insulin resistance [162].

There are six reported cases of IVF-induced HTG with secondary AP [166]. The pathophysiology of IVF-induced hypertriglyceridemia has not yet been clearly delineated but is most likely related to estrogen therapy.

Hypothyroidism

The hypothyroidism has been documented as a cause of HTG and HTG-induced AP [40, 167]. In

the general population, hypothyroidism is present in 1.4–13% of patients with hyperlipidemia [168]. Current guidelines from the *American Association of Clinical Endocrinologists* and the *American Thyroid Association* recommend screening for hypothyroidism in patients with newly diagnosed hyperlipidemia prior to starting a lipid-lowering agent [169, 170]. A low circulating free thyroid hormone level may impair LPL activity in adipose tissue raising LDL levels.

Medications

List of medications (Table 3.4) raises the serum TG level. Tamoxifen is known to cause a small, but significant decrease in high-density lipoprotein (HDL) cholesterol, unlike estrogen, which elevates HDL. In women with HTG, tamoxifen's ability to increase the TG level is especially pronounced, to an extent that may induce AP [162]. Clomiphene citrate is a synthetic estrogen analog with a biochemical structure similar to that of tamoxifen. Clomiphene elevates the TG level mainly in women with a predisposed risk for HTG, due to mutations in enzymes such as LPL [171]. Apoprotein E (apo E), particularly apo E allele 2, has been found in association with higher TG levels in pregnant patients with chylomicronemia [141]. There are many causes of secondary HTG (Table 3.4):

Table 3.4 Acquired/secondary causes of hypertriglyceridemia

Alcohol excess
High-carbohydrate diet
Insulin resistance
Obesity
Type II diabetes mellitus
Pregnancy
Chronic renal failure, nephrotic syndrome
Hypothyroidism
Cushing syndrome
Acute pancreatitis
Viral hepatitis
Biliary obstruction/cholestasis/biliary cirrhosis
Multiple myeloma, monoclonal gammopathy
Glycogen storage disease
Lipodystrophy
Systemic lupus erythematosus
Nephrotic syndrome
Chronic renal failure, uremia
Stress
Sepsis
Ileal bypass surgery

Drugs—exogenous estrogens, tamoxifen, glucocorticoids, β-blockers, amiodarone, thiazide diuretics, cyclosporine, retinoids, bile acid binding resins, antiretrovirals (protease inhibitors), propofol, clozapine, parenteral lipid infusion
Reproduced with permission from [172]

3.3.6 Alcohol Abuse

The role of alcohol in the etiopathogenesis and occurrence of AP is complex, but increased oxidative stress [173], disruption of cytosolic calcium homeostasis [174], and changes in gene expression [175] in the pancreas seem to be involved. Yet, only up to 5% of heavy alcohol drinkers (4–5 drinks/day) develop AP after 10–20 years [176]. It has been an ongoing discussion on whether the type of alcoholic beverage might influence the occurrence of AP. A potential role for the type of beverage was indicated showing a decline in the incidence of AP alongside a decline in the sales of spirits, despite increased sales of beer and wine [177]. The metabolism of ethanol is known to induce oxidative stress, which depletes cellular glutathione storage and results in lipid peroxidation and damage to pancreatic tissue [173]. However, in animal models, it seems that ethanol alone is not enough to induce AP [178]. Beer [179] and wine [179] include polyphenols with antioxidant capabilities. Other constituents in spirits such as long-chain alcohols have been shown to be more potent than ethanol in inducing oxidative stress [179]. Comparing the same amounts of alcohol, spirits deplete the antioxidant capacities more readily than beer or wine [179]. Thus, there might be other constituents in spirits that induce AP, in combination with ethanol or alone. Those drinking spirits might also have lower reserves of antioxidants at baseline, which could be depleted rapidly after intake of spirits. Alcohol use is associated with increased risk of AP, in a dose-dependent manner [180], but again consumed alcohol beverages contain other constituents that are a potential cause of injury of the pancreas. Therefore, the results should be carefully interpreted. Also, the patterns of drinking indicate that the more harmful the pattern of drinking (i.e., the more heavy drinking), the

higher the rates of alcohol-induced AP [181], with a threshold at approximately four drinks daily [182].

Another theory, from 1955, was that increase in intra-abdominal pressure is the most important event in the development of AP not only alcohol induced. It may be that the chronic alcoholic may hiccup inducing a pancreatic attack, by fixing his diaphragm and sending his bile juice up the pancreatic duct [32]. The constant increase of intra-abdominal pressure, especially in late pregnancy, could be additive to the risk of developing AP.

3.3.7 Medications

AP in general population due to medications is unusual, although the incidence may be increasing. Largest population-based series confirm the cause of AP in 0.3–1.4% in general population [183, 184]. Over 55 medications have been implicated, and the list continues to grow. Proposed criteria for classifying drugs as having an association with AP include the following [185]:

- AP develops during treatment with the drug
- Other likely causes of AP are not present
- AP resolves upon discontinuing the drug
- AP usually recurs upon readministration of the drug

Assignment to a particular category (definite, probable, or possible association) is often arbitrary due to inadequate and conflicting data and interpretation bias. The pathogenesis of drug-induced AP may be due to an *allergic response* (6-mercaptopurine, aminosalicylates, sulfonamides), a direct *toxic effect* (diuretics, sulfonamides, steroids), or *indirect effect* (codeine causes rapid but transient spasm of the sphincter of Oddi; some medications cause TG elevation).

Drug-induced AP in pregnancy is extremely rare [11]. Medications with the influence on estrogen activity are previously discussed (see Sect. 3.3.5.2). Medications associated with elevated TG that can cause AP through hypertriglyceridemia pathway include protease inhibitors, propofol, olanzapine, mirtazapine, and isotretinoin.

Gemeprost is a synthetic prostaglandin E1 (PGE_1) analog. PGE_1 increases pancreatic and mesenteric blood flow [186] and protein production. For instance, PGE_1 stimulated the production and secretion of α-amylase from the porcine pancreas in vitro [187] and enzyme output in dogs in vivo [186]. These facts would point out mifepristone or possibly gemeprost are possible causative agents during a medical abortion [188]. There is a problem with identification of a causative medication because these patients often receive other medications such as paracetamol or codeine (see further text).

Diuretics can induce AP [189, 190]. Preeclampsia-associated AP (see Sect. 3.3.10) is very rare and is associated with microvascular abnormalities that may involve cerebral, placental, hepatic, renal, and splanchnic circulation. It is likely that pancreatic vasculature is also altered and prone to AP. In one study, 66.7% of preeclampsia-associated AP received diuretics [12]. AP associated with angiotensin-converting enzyme inhibitors is thought to reflect angioedema of the gland. It is still not known whether preeclampsia/eclampsia, the therapy with diuretics, or its combination is the cause of AP during pregnancy.

List of medications that raise the serum TG level and other possible causes of AP in pregnancy are presented in Table 3.4.

3.3.8 Post-ERCP

See Sect. 2.2.5.4.

3.3.9 Pancreatic Neoplasms

AP may be a complication of pancreatic cancer as a result of infiltration of the pancreas by the tumor and/or obstruction of enzyme flow from the pancreatic duct/ampulla. Symptomatic pancreatic tumors during pregnancy are most commonly mucinous cystic neoplasms. First these are

the largest space-occupying pancreatic tumors, and, second, ovarian-like stroma exists exclusively in female patients with mucinous cystic neoplasms, which often is immunohistologically positive for progesterone and/or estrogen receptors. The physiological increase in blood concentration of these hormones could promote the progression of this type of tumors [95, 191]. One of the possibilities is that mucinous cystic neoplasms originate from primitive ovarian cells, which are incorporated into the embryonic pancreas when the left primordial gonad is in close proximity to the dorsal pancreatic anlage during embryogenesis [192]. The dorsal pancreatic anlage gives rise to the body and tail of the pancreas, and this hypothesis could explain the predilection of these tumors for the distal pancreas. Another possibility is that the neoplastic epithelial cells of these tumors might induce ovarian stromal differentiation in cells that normally reside in the pancreas. This concept is based on the fact that the stroma in the fetal pancreas is morphologically similar to that of mucinous cystic neoplasms [193].

Pancreatic mucinous cystic neoplasms present a clinical problem due to its malignant potential. Mucinous cystadenocarcinoma can arise de novo but also can be an evolution of the benign form. As large tumor size was reported to be one of the predictive factors of malignant forms, it is difficult to conclude whether this increased growth during pregnancy brings with it some degree of increased risk for malignant transformation [92]. It remains unclear whether high levels of estrogen and progesterone in pregnancy accelerate the malignant transformation of a benign tumor into a malignant tumor.

3.3.10 Preeclampsia/Eclampsia

A 25% incidence of preeclampsia has been observed in patients with PHPT [73] especially with parathyroid adenoma as a cause of PHPT [113, 194, 195]. Similarities in endothelial damage, insulin resistance, and cardiovascular disease shared between the PHPT and preeclampsia may support the hypothesis that a relationship exists between these two pathologic processes. In addition, maternal vitamin D deficiency has been associated with preeclampsia. This also supports the concept that the mechanisms that support calcium homeostasis affect blood pressure in the pregnant patient with preeclampsia [195].

Association between pregnancy-induced hypertension and dyslipidemia has clinical importance. The occurrence of metabolic syndrome in previous decades among women <20 years was 23.4%. These results, both with the high incidence of overweight and obesity, suggest the susceptibility of women of reproductive age to hypertensive disorders of pregnancy. The incidence of pregnancy-induced hypertension is severalfold higher in hyperlipidemic patients [196], and preeclampsia is preceded by raised serum triglyceride levels [197], in up to 50% of patients [196]. Cholesterol levels were not statistically different between cases and controls in any form of hypertension levels [197]. In preeclampsia, decidual vessels show fibrinoid necrosis of the vessel wall and focal accumulation of lipid-laden macrophages, similar to the situation in atherosclerosis, suggesting that enhanced lipid peroxidation may be involved in the foam cell formation. Preeclampsia is associated with microvascular abnormalities/alterations [198] that may involve cerebral, placental, hepatic, renal, and splanchnic circulation. It is likely that the pancreatic vasculature is also altered and prone to AP that often result in pancreatic necrosis [198]. It is difficult to conclude whether preeclampsia itself or in addition to diuretics causes AP, due to the high incidence of diuretics as a therapy for preeclampsia [12, 199] (see Sect. 3.3.7). Due to these interrelated metabolic pathways, with several factors that could cause AP in pregnancy, it is sometimes difficult to isolate single causative factor of AP during pregnancy.

3.3.11 Puerperium

Generally, AP can occur during any trimester but mostly during the third trimester; it is rarely seen in the postpartum period [11]. Most of the AP resolves during medical (or surgical) therapy, but

some are resolved only after CS when all the gestational (mostly hormonal) changes return to pregestational state. Partly it can be explained by lowered intra-abdominal or intrapancreatic pressure after delivery (see Sect. 3.3.6). Thus, AP associated with pregnancy usually occurs in young postpartum women and is usually due to gallstones (see Sect. 2.1.3). Speculation is that a few young women eject small gallstones from the gallbladder during the postpartum period when gallbladder contraction is restored, and some of these women develop an attack of AP. In contrast, in older women with reduced gallbladder contractility, most gallstones likely remain in the gallbladder until dissolved by less lithogenic bile. Three are no strict confirmation data on the role of biliary sludge in AP in pregnancy. No women with AP had documentation of biliary sludge, but the diagnosis of biliary sludge is often difficult, and prospective studies are needed. However, authors demonstrated that gallstones are the only etiology significantly associated with postpartum-related AP.

3.4 Clinical Presentation

AP presents essentially in the same way during pregnancy as in the nonpregnant state. However, it is difficult to diagnose AP by history taking and physical examination due to similarity to many acute abdominal conditions and due to maternal changes during pregnancy.

3.4.1 Medical History

All relevant information about possible causes should be obtained. The family history of hyperlipidemias, DM, AP, pregnancy-induced hypertension, preeclampsia/eclampsia, gallstones, etc. should be noted. These data should be noted and corrected before or during pregnancy planning to eliminate or minimize the possibility of AP during pregnancy. Since no safe level of alcohol has been established in pregnancy, it may not be socially acceptable for pregnant women to admit they consume alcohol. Assessing this risk accurately can be challenging. The T-ACE [Take (number of drinks), Annoyed, Cut down, Eye-opener], TWEAK (Tolerance, Worried, Eye-opener, Amnesia, Kut down), and AUDIT-C (AUDIT consumption) alcohol screening questionnaires show promise for use in pregnant women, but have not yet been validated as stand-alone tools in this population [200].

The symptoms of AP in pregnancy could be nonspecific; the predominant symptom is upper abdominal pain which is usually midepigastric and could radiate to the back in about 40% of the cases [11]. Pain is commonly accompanied by midepigastric tenderness, nausea, and vomiting [201]. Fever may be present [201]. These symptoms are common to all causes of AP. Some cases may have persistent vomiting, abdominal distention, and tenderness in the whole abdomen. The duration of symptoms may vary from 1 day up to 3 weeks. In severe cases, sinus tachycardia, hyperventilation, and the smell of acetone of the breath are also present. If accompanied by fever, unstable respiratory and circulatory function, shock, and gastrointestinal bleeding, these are strong indications for severe AP. Vomiting is a common symptom. Marcus in 1930 emphasized that persistent vomiting in pregnancy could be related to AP and that blood and enzyme studies should be done [202].

3.4.1.1 Primary Hyperparathyroidism

Truly asymptomatic PHPT in general population is rare when thorough anamnesis looks for subtle symptoms. Most frequent digestive manifestations are constipation, heartburn, nausea, and appetite loss that occur in 33%, 30%, 24%, and 15% of cases, respectively [203]. Unlike the general population, 4/5 of PHPT pregnant patients experience a clinically overt course [67, 72] with nephrolithiasis being the most frequent [67, 204]. Symptomatic PHPT is rarely detected in pregnancy due to the physiological changes that mask the symptoms; this includes maternal blood volume expansion, hypoalbuminemia, increased fetal calcium requirements, and increased calcium clearance. Between 23% and 80% of patients with PHPT are asymptomatic or to be more precise unrecognized [71, 77, 105].

The diagnosis should be suspected during pregnancy if the following conditions exist:

appropriate symptoms or signs (especially nephrolithiasis or AP), hyperemesis beyond the first trimester, history of recurrent spontaneous abortions/stillbirths or neonatal deaths, and neonatal hypocalcemia or tetany. Sometimes initial maternal presentation is due to complications which include hyperemesis gravidarum, preeclampsia, tremors, fractures, depression, headache, blurred vision, uremia, seizures, and coma [62, 67, 73].

> The most common indicator of PHPT during pregnancy is the development of neonatal tetany [62].

PHPT is considered as a risk factor for eclampsia [73, 205] which can also present during pregnancy with its symptoms and signs and mask PHPT.

3.4.1.2 Acute Fatty Liver of Pregnancy

Clinically, the onset is during the third trimester, most commonly between the 30th and 38th weeks of gestation. It is characterized by a nonspecific prodrome of symptoms. Sudden onset and persistent nausea and vomiting are the cardinal features (83%) [127]. Most patients with AFLP do not complain of right upper quadrant pain, which is in contrast to HELLP syndrome [127]. Vague abdominal pain, if present, is followed by jaundice. Complications include hepatic encephalopathy (13–50%), hypoglycemia (55%), acute renal failure (33–50%), coagulopathy (96%), disseminated intravascular coagulopathy (55%), preeclampsia (50%), and acute respiratory distress syndrome (17%) [127, 206]. Acute renal failure is most commonly in a form of acute tubular necrosis [127].

> Characteristic of AFLP is that abnormalities in renal dysfunction typically became evident after the abnormalities in liver dysfunction [127]. AP is typically noticed (radiographic and serum abnormalities) after the development of hepatic and renal dysfunction [98, 127].

3.4.1.3 Hypertriglyceridemia

Though the initial presentation of HTG-induced AP is similar to AP due to other etiologies, some features should lead to the consideration of HTG-induced AP. Poorly controlled DM, alcoholism, obesity, prior AP, and personal or family history of hyperlipidemia suggest HTG-induced AP [39, 43]. Alcoholism or DM has been reported in 72% of HTG-induced AP episodes [39, 43].

Medications

Drug-induced AP in general population has no distinguishing clinical features. A high index of suspicion and careful drug history are therefore essential for making the diagnosis. The time course of developing the disorder depends upon the drug involved. As an example, AP may develop within a few weeks after beginning a drug associated with an immunologically mediated adverse reaction; in this setting, the patient may also have a rash and eosinophilia. In contrast, patients taking valproic acid, pentamidine, or didanosine may not develop AP until after many months of use, presumably due to the chronic accumulation of toxic metabolic products. Proving the association with a particular drug may not always be straightforward, even in suspected cases. Thus, patients restarted on their medications should be closely monitored and the drug promptly discontinued if symptoms recur. It is known that many medications are discontinued during pregnancy by mothers themselves or by physicians when not sure about teratogenicity.

3.4.2 Physical Examination

Physical findings vary with the severity of illness; in moderate to severe AP, the patient appears acutely ill and is found lying in the “fetal position” with flexed knees, hips, and trunk. Abdominal tenderness is common; in diffuse peritonitis, muscle rigidity is present. Bowel sounds, secondary to paralytic ileus, are usually hypoactive or absent. Severe AP results in third-space fluid losses and systemic toxicity. Due to hypovolemia, tachycardia up to 150/min and low

blood pressure could be found. Also, because of the severe retroperitoneal inflammatory process, the temperature may increase. Dyspnea, tachypnea, and shallow respirations resulting in hypoxemia may be present.

Clinical signs are the same as in nonpregnant population. Cullen's sign (Fig. 3.7) and Grey Turner's sign are rare but among the most common as in general population (present in 2%). Other signs are *Fox's sign* (ecchymosis of the upper thigh with superior border) and *Stabler's sign* (bruising of the groin). Differential diagnosis of the diseases coexistent with non-iatrogenic Cullen's sign is presented in Table 15.2.

Some physical findings point to a specific cause of AP: jaundice in biliary origin, spider angiomas in alcoholic, or xanthomata and lipemia retinalis in hyperlipidemic AP. HTG can lead to chylomicronemia syndrome, which can manifest with eruptive xanthomata over extensor surfaces of the arms, legs, buttocks, and back indicating triglyceride levels greater than 1000 mg/dL (Fig. 3.8) [55, 208], lipemia retinalis (Fig. 3.9a), and hepatosplenomegaly from fatty infiltration of the liver [55, 208, 209]. Lipemia retinalis should be distinguished from Purtscher-like retinopathy (Fig. 3.9b) found in AP, preeclampsia, and childbirth (and other nontraumatic conditions). It is associated with a constellation of retinal findings including cotton-wool spots, retinal hemorrhages, optic disc edema, and *Purtscher flecken* (areas of inner retinal whitening).

Sometimes the cause of the AP can be found during emergent operation for acute abdomen.

Fig. 3.7 Cullen's sign. Reproduced with permission from [207]

Intraperitoneal fluid can be milky and lipemic. Similarly, if the emergent CS is indicated, the placenta can appear to be covered with milky fluid (Fig. 3.10) which contribute to the diagnosis of hyperlipidemic AP [212].

3.5 Diagnosis

When AP is suspected on clinical grounds, laboratory investigations and imaging modalities are mandatory. Some important normal laboratory values in pregnant and nonpregnant women are compared in Table 3.5. Serum total calcium, PTH, and 25-hydroxyvitamin D values do not change during pregnancy, while 1,25-dihydroxyvitamin D and PTH-related protein have increased values [213]. Before 1951, the vast majority of diagnoses were made during operation or an autopsy. In only 5.7% the diagnosis was made on clinical grounds [4]. Around 15% of pancreatic pseudocysts were diagnosed at emergency laparotomy [54]. With modern imaging techniques currently, all pancreatic pseudocysts are discovered prior to surgery.

3.5.1 Laboratory Findings

3.5.1.1 Liver and Pancreatic Enzymes

Marcus in 1930 is credited with the first clinical diagnosis of AP in pregnancy with the aid of diastase and amylase studies [208]. Pregnancy-related hematological and biochemical alterations interfere with the interpretation of diagnostic tests and assessment of severity of AP (Table 3.5). In normal pregnant subjects, low amylase levels are most frequent between the 8th and 16th week but rise steadily in the later months, reaching the normal range at full term [215, 216].

> Laboratory investigations are the same as in nonpregnant and rely on at least a threefold elevation of serum amylase and lipase levels.

Fig. 3.8 Clinical manifestations of hyperlipidemia. (**a**) Achilles tendon xanthoma (heterozygous familial hypercholesterolemia – type IIa); (**b**) tendon xanthomata on dorsum of the hand (heterozygous familial hypercholesterolemia); (**c**) subperiosteal xanthomata (heterozygous familial hypercholesterolemia); (**d**) planar xanthoma in antecubital fossa (homozygous familial hypercholesterolemia); (**e**) striate palmar xanthomata (type III); (**f**) tuberoeruptive xanthomata on elbow and extensor surface of arm (type III); (**g**) milky plasma from patient with acute abdominal pain (severe hypertriglyceridemia); (**h**) eruptive xanthomata on extensor surface of the forearm (severe hypertriglyceridemia). Reproduced with permission from [209]

The total serum amylase level rises within 6–12 h of onset of the disease, usually remains elevated for 3–5 days. Serum lipase is elevated on the first day of and remains elevated for up to 2 weeks. In terms of diagnostic accuracy, specificity, and sensitivity in general population, lipase is superior to amylase [217, 218] despite not being absolutely specific to the pancreas. Enzyme concentrations are similar in nonpregnant and pregnant women and an increase in either is suggestive of AP in pregnancy [219]. Elevation of serum alanine aminotransferase levels to >3 times the upper limit of normal is a very sensitive for biliary AP in the nonpregnant population [220] and should be also suspected in pregnancy. The dynamics of amylase rise and fall depends on the severity and extension of pancreatic damage itself, but it is unknown whether the cause of

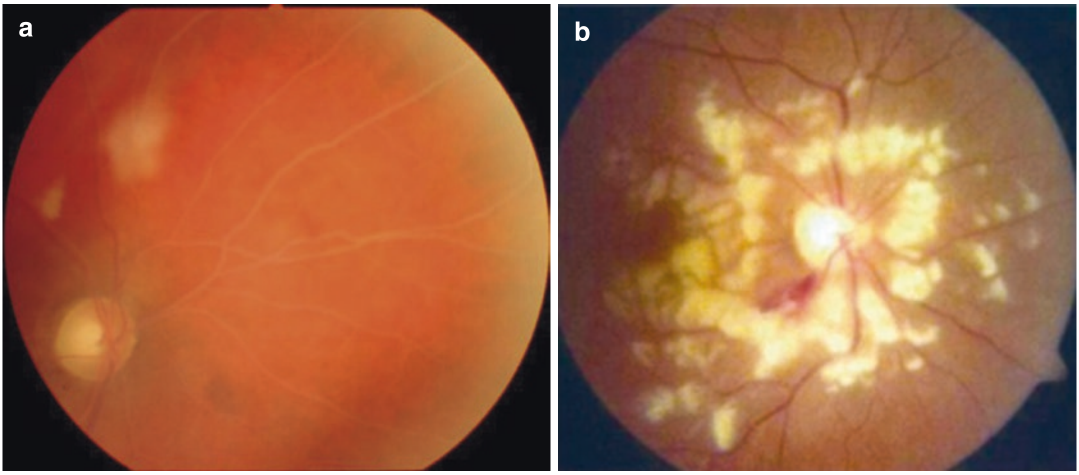

Fig. 3.9 (*left*) Lipemia retinalis associated with hyperlipidemia. Rare and asymptomatic creamy white appearance of retinal vessels occurs when triglyceride value reaches more than 2000 mg/dL (22.6 mmol/L) – the effect due to dispersion of light caused by high value of circulating chylomicrons in the blood, most commonly occurring in familial hyperchylomicronemia (reproduced from [210] under the CC BY 3.0). It should be distinguished from (*right*) Purtscher-like retinopathy found in acute pancreatitis and preeclampsia. Reproduced with permission from [211]

Fig. 3.10 Placenta covered with milky fluid suggestive of severely increased serum lipid levels. Reproduced from [212] under the CC Attribution License

AP changes the curve of amylase rise and fall (Fig. 3.11).

AP could not be ruled out if normal level of serum amylase is detected. One reason is that the serum amylase may not increase with extensive pancreatic necrosis. Also, precise values of amylase and some other laboratory parameters are not reliable with a significant increase in plasma TG levels (see Sect. 3.5.1.1). So, in nonpregnant patients, normal amylase levels usually exclude the diagnosis of AP, with the exception of hyperlipidemic AP, acute exacerbation of chronic pancreatitis, and examinations in the delayed course of AP [222]. Therefore, the urine amylase level may be more helpful. Caution in the interpretation of serum amylase and urinary diastase determination should be exercised if morphine has been given. Morphine causes spasm of the sphincter of Oddi with obstruction of the pancreatic drainage.

No enzyme assay has a predictive role in determining the severity or etiology of AP in pregnancy [223].

Once the diagnosis of AP is established, daily measurements of enzymes have no value in assessing the clinical progress of the patient or ultimate prognosis. A persistently raised serum amylase activity may suggest the presence of a pancreatic pseudocyst. For the early postpartum period, there are no data available about amylase and lipase dynamics due to the extreme rarity.

Table 3.5 Calculated upper (97.5 percentile) and lower (2.5 percentile) limits for the reference interval and 90% confidence intervals (in brackets) during different stages of pregnancies and postpartum. The samples denoted as predelivery were collected 0–14 days prior to delivery. Postpartum samples were collected at least 45 days after delivery

	Lower limit	Upper limit
Alanine aminotransferase (ALT) (µkat/L)		
Week 7–17	<0.15[a]	0.50 (0.41–0.58)
Week 17–24	<0.15[a]	0.55 (0.49–0.61)
Week 24–28	<0.15[a]	0.54 (0.44–0.63)
Week 28–31	<0.15[a]	0.39 (0.37–0.40)
Week 31–34	<0.15[a]	0.42 (0.38–0.46)
Week 34–38	<0.15[a]	0.41 (0.38–0.44)
Predelivery	<0.15[a]	0.36 (0.33–0.39)
Postpartum	0.19 (0.17–0.20)	1.10 (1.00–1.19)
Albumin (g/L)		
Week 7–17	32.2 (30.9–33.5)	43.2 (42.6–43.8)
Week 17–24	27.9 (27.4–28.4)	36.9 (36.4–37.3)
Week 24–28	27.0 (26.5–27.4)	34.6 (33.8–35.4)
Week 28–31	25.1 (24.3–25.9)	33.7 (33.3–34.0)
Week 31–34	24.4 (23.5–25.3)	33.7 (33.1–34.3)
Week 34–38	23.1 (21.9–24.4)	33.8 (32.5–35.2)
Predelivery	24.0 (23.0–24.9)	38.2 (34.4–42.0)
Postpartum	37.0 (36.4–37.6)	47.2 (46.6–47.8)
Alkaline phosphatase (µkat/L)		
Week 7–17	0.58 (0.53–0.63)	1.33 (1.20–1.46)
Week 17–24	0.65 (0.63–0.68)	1.75 (1.37–2.14)
Week 24–28	0.77 (0.74–0.81)	1.92 (1.66–2.18)
Week 28–31	0.88 (0.78–0.98)	1.98 (1.75–2.21)
Week 31–34	1.11 (1.02–1.20)	2.96 (2.55–3.36)
Week 34–38	1.46 (1.23–1.68)	3.81 (3.41–4.21)
Predelivery	1.64 (1.37–1.91)	4.95 (4.70–5.19)
Postpartum	0.87 (0.69–1.04)	2.74 (2.30–3.18)
Amylase (pancreas) (µkat/L)		
Week 7–17	0.22 (0.19–0.25)	0.73 (0.65–0.81)
Week 17–24	0.26 (0.23–0.29)	0.78 (0.69–0.86)
Week 24–28	0.25 (0.20–0.30)	0.84 (0.67–1.00)
Week 28–31	0.25 (0.21–0.29)	0.66 (0.62–0.70)
Week 31–34	0.24 (0.19–0.29)	0.93 (0.80–1.05)
Week 34–38	0.25 (0.20–0.30)	0.82 (0.76–0.87)
Predelivery	0.25 (0.20–0.27)	0.70 (0.61–0.79)
Postpartum	0.25 (0.23–0.28)	0.65 (0.60–0.70)
Apolipoprotein A1 (g/L)		
Week 7–17	1.16 (1.00–1.31)	2.47 (2.21–2.74)
Week 17–24	1.48 (1.40–1.56)	2.53 (2.46–2.60)
Week 24–28	1.51 (1.41–1.61)	2.47 (2.39–2.55)
Week 28–31	1.43 (1.16–1.70)	2.56 (2.49–2.63)
Week 31–34	1.40 (1.14–1.65)	2.69 (2.58–2.81)
Week 34–38	1.45 (1.34–1.55)	2.62 (2.46–2.77)
Predelivery	1.32 (1.11–1.53)	2.68 (2.50–2.86)
Postpartum	1.17 (1.11–1.23)	2.00 (1.93–2.05)
Apolipoprotein B (g/L)		
Week 7–17	0.53 (0.51–0.56)	1.23 (1.17–1.30)
Week 17–24	0.66 (0.60–0.71)	1.88 (1.65–2.10)
Week 24–28	0.67 (0.55–0.79)	2.27 (1.96–2.57)
Week 28–31	0.73 (0.64–0.81)	2.32 (2.06–2.58)
Week 31–34	0.81 (0.62–1.00)	2.62 (2.21–3.02)
Week 34–38	0.85 (0.78–0.93)	2.38 (2.22–2.53)
Predelivery	0.75 (0.63–0.87)	2.50 (2.38–2.61)
Postpartum	0.52 (0.40–0.63)	1.37 (1.29–1.45)
AST (µkat/L)		
Week 7–17	0.15 (0.13–0.18)	0.66 (0.57–0.76)
Week 17–24	0.17 (0.15–0.18)	0.55 (0.48–0.62)
Week 24–28	0.19 (0.17–0.20)	0.56 (0.44–0.68)
Week 28–31	0.19 (0.16–0.21)	0.47 (0.43–0.50)
Week 31–34	0.21 (0.19–0.23)	0.49 (0.47–0.51)
Week 34–38	0.21 (0.20–0.22)	0.53 (0.46–0.59)
Predelivery	0.22 (0.21–0.24)	0.56 (0.52–0.60)
Postpartum	0.15 (0.12–0.18)	0.70 (0.67–0.73)
Bilirubin (µmol/L)		
Week 7–17	3.5 (<3.0–4.4)	22.4 (18.8–26.0)
Week 17–24	<3.0[a]	13.9 (12.2–15.6)
Week 24–28	<3.0[a]	17.8 (14.3–21.4)
Week 28–31	<3.0[a]	19.7 (15.4–24.1)
Week 31–34	<3.0[a]	17.1 (15.0–19.2)
Week 34–38	<3.0[a]	18.6 (15.7–21.4)
Predelivery	<3.0[a]	19.4 (14.9–23.9)
Postpartum	3.3 (<3.0–3.8)	30.9 (22.8–39.0)
Calcium (mmol/L)		
Week 7–17	2.18 (2.12–2.23)	2.53 (2.50–2.57)
Week 17–24	2.08 (2.04–2.11)	2.45 (2.41–2.50)
Week 24–28	2.04 (1.99–2.08)	2.40 (2.36–2.43)
Week 28–31	2.07 (2.03–2.11)	2.41 (2.33–2.49)
Week 31–34	2.05 (1.99–2.10)	2.38 (2.37–2.40)
Week 34–38	2.04 (1.96–2.11)	2.41 (2.39–2.43)
Predelivery	1.98 (1.91–2.05)	2.46 (2.42–2.50)
Postpartum	2.06 (1.90–2.22)	2.57 (2.51–2.63)
Chloride (mmol/L)		
Week 7–17	100 (100–101)	107 (107–107)
Week 17–24	97 (97–100)	107 (107–107)
Week 24–28	99 (97–100)	108 (108–109)
Week 28–31	99 (97–100)	108 (108–109)
Week 31–34	97 (95–100)	108 (107–108)
Week 34–38	97 (95–100)	109 (107–110)
Predelivery	95 (91–99)	108 (107–108)
Postpartum	100 (100–101)	108 (107–109)
Creatinine (µmol/L)		
Week 7–17	36 (34–39)	62 (61–63)
Week 17–24	34 (31–38)	58 (57–59)
Week 24–28	32 (27–36)	62 (60–63)
Week 28–31	32 (28–36)	56 (55–58)
Week 31–34	34 (32–36)	58 (57–60)
Week 34–38	33 (31–36)	60 (56–64)
Predelivery	31 (25–36)	72 (67–78)
Postpartum	48 (43–53)	86 (79–93)

Table 3.5 (continued)

	Lower limit	Upper limit
Cyc-C (mg/L)		
Week 7–17	0.41 (0.39–0.43)	0.62 (0.61–0.64)
Week 17–24	0.46 (0.45–0.46)	0.71 (0.68–0.73)
Week 24–28	0.47 (0.44–0.50)	0.76 (0.74–0.78)
Week 28–31	0.50 (0.48–0.51)	0.82 (0.79–0.84)
Week 31–34	0.50 (0.46–0.55)	0.98 (0.94–1.02)
Week 34–38	0.58 (0.53–0.63)	1.30 (1.23–1.37)
Predelivery	0.63 (0.53–0.73)	1.70 (1.36–2.04)
Postpartum	0.54 (0.49–0.59)	1.00 (0.93–1.07)
Ferritin (μg/L)		
Week 7–17	7.1 (6.3–7.9)	106.4 (83.9–128.9)
Week 17–24	4.1 (3.1–5.1)	65.6 (46.5–84.7)
Week 24–28	3.8 (3.0–4.6)	49.8 (37.9–61.6)
Week 28–31	4.2 (3.9–4.5)	39.0 (29.5–48.5)
Week 31–34	4.3 (3.9–4.7)	40.5 (33.8–47.2)
Week 34–38	4.8 (4.3–5.2)	43.5 (38.7–48.2)
Predelivery	5.0 (4.1–6.0)	60.5 (57.5–63.4)
Postpartum	6.9 (4.7–9.1)	139.0 (103.1–174.8)
GGT (μkat/L)		
Week 7–17	0.12 (0.11–0.13)	0.58 (0.52–0.64)
Week 17–24	0.09 (0.08–0.10)	0.36 (0.31–0.40)
Week 24–28	0.09 (0.08–0.10)	0.40 (0.34–0.47)
Week 28–31	0.09 (0.07–0.10)	0.41 (0.35–0.47)
Week 31–34	0.08 (0.06–0.10)	0.43 (0.40–0.46)
Week 34–38	0.09 (0.07–0.11)	0.40 (0.32–0.48)
Predelivery	0.09 (0.07–0.10)	0.65 (0.47–0.83)
Postpartum	0.11 (0.10–0.12)	0.58 (0.38–0.78)
Iron (μmol/L)		
Week 7–17	8.7 (6.9–10.5)	37.0 (34.5–39.5)
Week 17–24	7.9 (4.8–10.9)	31.9 (29.1–34.7)
Week 24–28	8.0 (4.7–11.3)	50.0 (37.6–62.3)
Week 28–31	7.6 (6.6–8.7)	37.5 (31.8–43.2)
Week 31–34	6.9 (5.6–8.2)	36.4 (30.4–42.3)
Week 34–38	7.6 (7.3–7.9)	34.5 (31.7–37.3)
Predelivery	8.0 (5.5–10.6)	32.9 (29.8–36.0)
Postpartum	7.9 (6.8–9.1)	30.1 (25.3–34.9)
LDH (μkat/L)		
Week 7–17	1.60 (1.58–1.63)	5.72 (3.57–7.86)
Week 17–24	1.38 (1.24–1.51)	2.52 (2.42–2.63)
Week 24–28	1.28 (1.13–1.42)	3.11 (2.59–3.64)
Week 28–31	1.37 (1.13–1.49)	2.87 (2.51–3.24)
Week 31–34	1.42 (1.36–1.49)	3.17 (2.74–3.60)
Week 34–38	1.41 (1.34–1.48)	2.55 (2.48–2.61)
Predelivery	1.64 (1.60–1.67)	2.80 (2.74–2.86)
Postpartum	1.58 (1.48–1.68)	3.43 (3.07–3.78)
Magnesium (mmol/L)		
Week 7–17	0.70 (0.69–0.71)	0.96 (0.88–1.059)
Week 17–24	0.66 (0.65–0.66)	0.87 (0.84–0.90)
Week 24–28	0.63 (0.63–0.63)	0.91 (0.86–0.97)
Week 28–31	0.63 (0.63–0.64)	0.91 (0.88–0.94)
Week 31–34	0.64 (0.64–0.64)	0.90 (0.84–0.97)
Week 34–38	0.57 (0.50–0.65)	0.87 (0.84–0.90)
Predelivery	0.64 (0.63–0.65)	0.94 (0.91–0.96)
Postpartum	0.68 (0.66–0.71)	0.99 (0.92–1.06)
Phosphate (mmol/L)		
Week 7–17	0.85 (0.80–0.90)	1.65 (1.43–1.86)
Week 17–24	0.84 (0.74–0.95)	1.45 (1.41–1.48)
Week 24–28	0.81 (0.67–0.95)	1.47 (1.43–1.51)
Week 28–31	0.77 (0.70–0.85)	1.44 (1.38–1.49)
Week 31–34	0.84 (0.72–0.95)	1.42 (1.35–1.49)
Week 34–38	0.85 (0.80–0.90)	1.45 (1.41–1.50)
Predelivery	0.89 (0.86–0.92)	1.50 (1.43–1.57)
Postpartum	1.00 (0.89–1.12)	1.80 (1.62–1.99)
Potassium (mmol/L)		
Week 7–17	3.24 (3.14–3.35)	4.86 (4.61–5.12)
Week 17–24	3.26 (3.06–3.45)	4.60 (4.49–4.72)
Week 24–28	3.27 (3.17–3.38)	4.62 (4.57–4.68)
Week 28–31	3.46 (3.40–3.52)	4.74 (4.54–4.93)
Week 31–34	3.30 (3.16–3.44)	5.16 (4.99–5.33)
Week 34–38	3.32 (3.19–3.46)	5.09 (4.75–5.43)
Predelivery	3.41 (3.35–3.47)	5.46 (5.23–5.68)
Postpartum	3.48 (3.41–3.55)	5.06 (4.88–5.23)
Sodium (mmol/L)		
Week 7–17	133.2 (131.7–134.7)	140.5 (139.5–141.5)
Week 17–24	128.5 (127.3–129.8)	140.0 (139.5–140.5)
Week 24–28	129.2 (127.7–130.7)	139.3 (139.1–139.5)
Week 28–31	129.9 (128.2–131.6)	140.2 (138.7–141.7)
Week 31–34	127.0 (122.9–131.1)	139.1 (139.0–139.3)
Week 34–38	127.0 (123.2–130.7)	140.2 (139.3–141.2)
Predelivery	124.0 (120.6–127.4)	140.4 (139.3–141.4)
Postpartum	134.0 (132.4–135.7)	143.8 (143.5–144.1)
Transferrin (g/L)		
Week 7–17	1.92 (1.76–2.08)	3.85 (3.44–4.26)
Week 17–24	2.20 (2.04–2.36)	4.34 (4.14–4.54)
Week 24–28	2.72 (2.68–2.77)	4.36 (4.23–4.50)
Week 28–31	2.86 (2.82–2.91)	4.78 (4.69–4.88)
Week 31–34	2.94 (2.86–3.02)	5.09 (5.05–5.13)
Week 34–38	2.88 (2.76–3.00)	5.12 (4.72–5.52)
Predelivery	2.59 (2.47–2.71)	5.53 (0.47–0.83)
Postpartum	1.73 (1.54–1.91)	3.39 (3.07–3.71)
Triglycerides (mmol/L)		
Week 7–17	0.55 (0.46–0.63)	3.08 (2.21–3.95)
Week 17–24	0.89 (0.73–1.05)	4.32 (3.76–4.89)
Week 24–28	1.09 (0.92–1.25)	3.63 (3.32–3.94)
Week 28–31	1.12 (0.96–1.29)	4.98 (4.27–5.69)
Week 31–34	1.52 (1.41–1.62)	4.79 (4.15–5.43)
Week 34–38	1.62 (1.28–1.97)	5.12 (4.72–5.52)
Predelivery	1.51 (1.29–1.72)	5.87 (5.22–6.52)

(continued)

Table 3.5 (continued)

	Lower limit	Upper limit
Postpartum	0.51 (0.48–0.54)	3.53 (2.75–4.32)
TSH (mU/I)		
Week 7–17	0.09 (0.00–0.26)	3.39 (3.02–3.76)
Week 17–24	0.37 (0.24–0.49)	3.40 (2.62–4.19)
Week 24–28	0.39 (0.27–0.51)	3.88 (3.27–4.50)
Week 28–31	0.23 (0.00–0.48)	2.83 (2.65–3.02)
Week 31–34	0.40 (0.26–0.53)	3.88 (3.18–4.59)
Week 34–38	0.38 (0.24–0.51)	4.04 (2.95–5.13)
Predelivery	0.78 (0.52–1.04)	5.33 (4.28–6.39)
Postpartum	0.22 (0.00–0.49)	3.19 (2.67–3.70)
Urate (μmol/L)		
Week 7–17	121.3 (105.3–137.3)	314.2 (278.9–349.5)
Week 17–24	147.8 (130.2–165.4)	293.9 (274.3–313.6)
Week 24–28	143.2 (122.2–164.3)	318.8 (299.0–338.5)
Week 28–31	137.5 (113.8–161.3)	289.2 (283.6–294.9)
Week 31–34	153.5 (139.9–167.0)	353.7 (327.2–380.3)
Week 34–38	185.9 (176.8–195.0)	373.4 (345.5–401.3)
Predelivery	202.3 (185.4–219.3)	401.2 (385.6–416.7)
Postpartum	175.3 (142.2–208.3)	437.9 (417.3–458.6)
Urea (mmol/L)		
Week 7–17	2.07 (1.93–2.21)	4.21 (3.97–4.45)
Week 17–24	1.66 (1.36–1.96)	4.50 (4.07–4.94)
Week 24–28	1.60 (1.32–1.87)	4.18 (4.05–4.32)
Week 28–31	1.51 (1.12–1.90)	3.63 (3.29–3.96)
Week 31–34	1.72 (1.62–1.83)	3.65 (3.55–3.75)
Week 34–38	1.70 (1.66–1.74)	3.97 (3.88–4.05)
Predelivery	1.62 (1.43–1.81)	4.88 (4.66–5.11)
Postpartum	2.80 (2.24–3.37)	7.17 (6.80–7.53)

[a]The 90% confidence interval could not be calculated as the instrument did not report AIT values <0.15 μkat/L and bilirubin values <3.0 and several test results were <0.15 and <3.0, respectively.
Reproduced with permission from [214]

Liver tests in pregnant women with biliary AP are frequently normal. The transaminase levels are less than 5× the upper normal limits in 89% of patients and less than 3× the upper normal limits in 80% of patients. Possibly the increased metabolism of maternal transaminases by the placenta leads to relatively normal maternal levels of liver enzymes [27].

Laboratory abnormalities consistent with AFLP include mild elevation of ALT and AST to 200–300 IU/L [224], prolongation of prothrombin time and partial thromboplastin time, decreased fibrinogen, acute renal failure, severe hypoglycemia, a bilirubin level of 1–10 mg/dL, and leukocytosis. In pregnant women with AP and AFLP, elevated serum lipase levels are present in 91% [127]. The diagnosis of LCHAD deficiency in newborns can save lives; therefore, all women with AFLP and their children should be administered a molecular test for LCHAD, which should at least evaluate the most common mutation, namely, G1528C [225, 226].

Gamma-glutamyl transpeptidase (GGT) levels either are unchanged or fall slightly during gestation. An elevated GGT level can help us to evaluate the history of alcohol use during pregnancy as patients might not be coming forth, due to stigmata associated with it [227].

3.5.1.2 Serum Lipids

HTG-induced AP is conventionally thought to be triggered when TG levels exceed 1000 mg/dL (10 mmol/L) unless accompanied by lactescent (milky coloration) serum [39, 161], found in 45% of patients [39]. In severe HTG (serum TG level > 2000 mg/dL), there is a significant risk of AP [228]. Normal lipidogram across pregnancy is presented in Fig. 3.4. Chylomicrons are formed at these high TG levels and serum becomes lactescent. TG values of even 3810 mg/dL were encountered [229]. In contrast, mild to moderate elevations in TGs (2–10 mmol/L) are extremely common in the early phase of AP of any etiology. One study noted such elevations in 47% of randomly selected patients presenting with AP [48]. Mild to moderate elevations of TGs were felt more likely to be an epiphenomenon of the AP rather than a true causal precipitant [48]. It is important to remember that chylomicrons are the product of dietary fat absorption. Enforced abstinence from eating after a diagnosis of pancreatitis may allow rapid metabolism of the TG-rich chylomicrons. Severe elevations (>20 mmol/L) were found in 10% of patients, but levels rapidly fell in the majority of patients within 72 h of presentation; therefore, a delay in the presentation or consideration of diagnosis can lead to false conclusions about etiology. TG levels remained

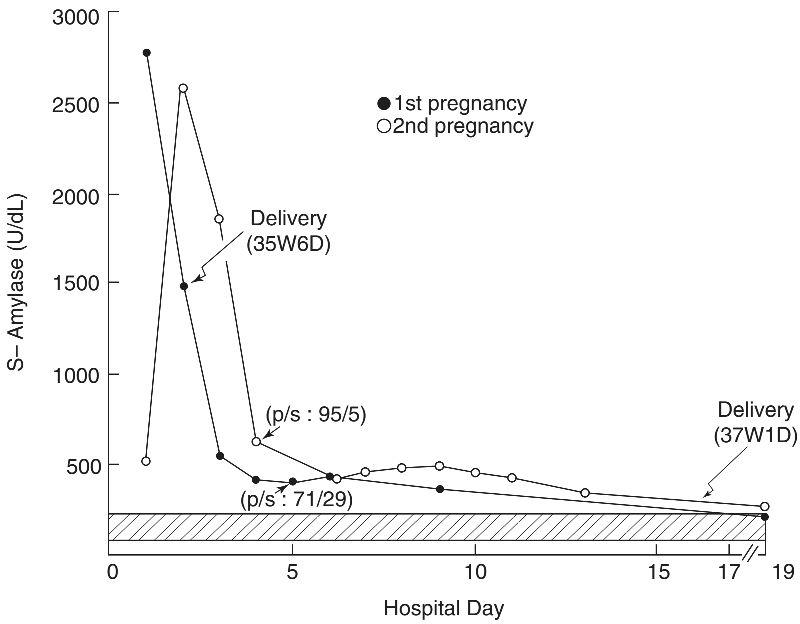

Fig. 3.11 Changes in the serum amylase level during hospital admission. Shaded horizontal area indicates the normal range for serum amylase. P/S, ratio of pancreas to salivary amylase isozymes. Reproduced with permission from [221]

mildly elevated for up to 15 days, probably reflecting an underlying lipid disorder [48]. Some recommend that a lipemic blood sample found at any stage during pregnancy should be considered as potentially indicative of partial LPL deficiency [230]. Lipid analysis requires direct measurement through centrifugation or immunoprecipitation.

3.5.1.3 Serum Calcium and Parathormone

> Serum calcium levels should be obtained in any pregnant woman with persistent significant nausea, vomiting, and abdominal pain, especially when AP is suspected [231].

PHPT is diagnosed with an elevated calcium and elevated or normal intact PTH level [232]. Maternal serum calcium falls by about 10% in pregnancy; therefore when evaluating calcium, it may be prudent to draw an ionized calcium. During pregnancy, there is an increase in extracellular volume and a 20% decrease in albumin, which may result in a factitiously low calcium (lower 10%), whereas the ionized calcium remains unchanged [194]. Intact serum PTH represents the N-terminal fragment of PTH. This is the recommended level to draw given the C-terminal or standard PTH level can be falsely elevated in patients with renal impairment due to the extended half-life and may be mildly elevated in the elderly [67]. An elevated serum PTH level does not necessarily indicate PHPT (especially in pregnant women), and a normal level does not exclude it. Therefore, the serum PTH level must be evaluated as a function of the serum calcium level. Patients with hypercalcemia who have normal renal function and an elevated serum PTH level almost certainly have primary HPT. However, even when the serum PTH level is normal in these patients, PHPT should still be suspected since hypercalcemia should suppress parathyroid gland function and reduce the serum PTH level to below normal. It is, therefore, the presence of detectable amounts of PTH in the blood of patients with hypercalcemia that is compatible with PHPT. It may be that in the patients with normal PTH levels, the PTH molecule has undergone cleavage by the liver and kidney so that its levels in the peripheral veins are reduced. Measurement of the fasting serum phosphate (hypophosphatemia, <2.5 mg/dL), as well as of the urinary cyclic adenosine monophosphate levels, should help in the recognition of

PHPT. A cutoff level of a total serum calcium concentration greater than 10.1 mg/dL (2.52 mmol/L) during the second or 8.8 mg/dL (2.2 mmol/L) during the third trimester is diagnostic for PHPT. Hypercalcemia with values higher than 13 mg/mL in the presence of a palpable neck mass should raise a strong suspicion of parathyroid carcinoma.

Hypercalcemia should be suspected when attempts to obtain coagulation profile results are unsuccessful because multiple serum samples are clotted and could not be analyzed. Calcium is required for coagulation factors to bind to phospholipids, and this binding is typically arrested in laboratory studies with sodium citrate. For a typical laboratory specimen, whole blood is collected using a test tube with a fixed amount of sodium citrate, in the ratio of one part citrate solution to nine parts of whole blood. Before analysis, a fixed amount of calcium is added back to the sample to bind to the citrate in the tube, allowing clotting studies to be evaluated. The amount of citrate in collection tubes accounts for normal ranges of calcium. In severe hypercalcemia, there is no standardized method for adding citrate solution to overcome it, and results are not standardized or validated. Therefore, evaluations of coagulation studies are deferred until patient's serum calcium is lowered. Coagulopathy is excluded based on stable platelet studies, a peripheral smear without evidence of schistocytes and thromboelastography and no evidence of clinical bleeding.

PHPT has been noted in 20–30% of the patients demonstrating multiple endocrine neoplasia (MEN) type IIa [233].

> Any patient diagnosed with PHPT during pregnancy should be investigated for signs of the MEN-IIa syndrome.

3.5.1.4 Other Serum Markers

At present, serum CRP at 48 h is the best available laboratory marker of AP severity. Urinary trypsinogen activation peptides within 12–24 h of onset of AP are able to predict the severity but are not widely available.

Patients with AP, examined within 48–72 h after onset of their illness, have fasting hyperglycemia, hyperglucagonemia, and relative hypoinsulinemia. With recovery from the acute episode, these changes gradually reverse, reaching normal by about 15 days [234]. Therefore, it is not always clear whether the pregnant patient has gestational DM or is hyperglycemia the result of AP. Serum glucose levels should be checked several weeks and months after the episode of AP and OGTT made if not performed during pregnancy before the attack of AP.

3.5.1.5 Confounding Laboratory Findings

Amylase/Lipase

In general population, 16–25% of patients with diabetic ketoacidosis may have elevated pancreatic enzymes and TGs, circumstance less reliable diagnosis of AP based only on biochemical parameters [235]. The rise of amylase and lipase levels exceeded the expected increased values due to the slight reduction of the renal function in the preeclamptic but indicates a possible concomitant injury of the pancreas [236].

Triglycerides

Elevated TG levels can alter serum levels of sodium, serum amylase, and LDL. Pseudohyponatremia results in the excess TG which displace water-containing sodium [237]. Ultracentrifugation is needed to separate the aqueous phase and measure the true sodium level [237]. HTG levels >500 mg/dL may cause a falsely normal amylase due to interference with a calorimetric reading of the assay or presence of an interfering inhibitor. Although the exact inhibitor is not known, it does not seem to be TG itself, as the removal of excess serum lipids by ultracentrifugation does not eliminate the inhibition of amylase activity [238]. Lipemia may affect an automated analysis of other parameters, such as glucose, liver enzymes, urea, creatinine, total bilirubin, etc. by altering light scattering, increasing the nonaqueous phase, and partitioning between the polar and nonpolar phases [239]. This problem can be partially overcome by assaying serial sample dilutions [43, 238] or measur-

ing *serum lipase or amylase to creatinine ratio* (ratio greater than 5% suggests AP) [240], neither of which is affected by HTG [43].

Friedewald eq. [LDL-C in mg/dL = TC − HDL-C−(TG/5), LDL-C in mmol/L =TC − HDL-C−(TG/2.2)] used to determine LDL from TG levels lose accuracy with high TG levels [241]; a commonly accepted upper limit is 400 mg/dL [242].

One of the most clinically relevant sources of variability is the presence of intercurrent illness with acute phase inflammation because the associated inflammatory response modifies the lipid and lipoprotein profile. Acute inflammation increases VLDL (TG) and reduces HDL-C and LDL-C. It is important to note that the lipoprotein response to intercurrent illness shares some of the features of that associated with DM type II. The magnitude of modifications is usually proportional to the severity of the underlying illness [243], but proportionately smaller responses should also be anticipated in association with minor intercurrent illnesses. Therefore HTG causes AP while AP can additionally increase the serum levels of TG creating the vicious cycle.

Parathyroid Hormone

Parathyroid hormone levels may be falsely lowered due to hypoalbuminemia or suppressed by magnesium tocolysis [82].

3.5.1.6 Ranson Criteria

There are several scoring systems in general population not for the diagnosis but for the prognosis of AP. The most common in general population, Ranson scoring system, is calculated in several case reports but is not validated in pregnancy [244, 245].

3.5.2 Transabdominal Ultrasound

Transabdominal ultrasound (US) is the initial imaging technique of choice to confirm the AP per se (Fig. 3.12) and to identify or exclude biliary etiology, the finding on which further diagnostic workup and therapy depend

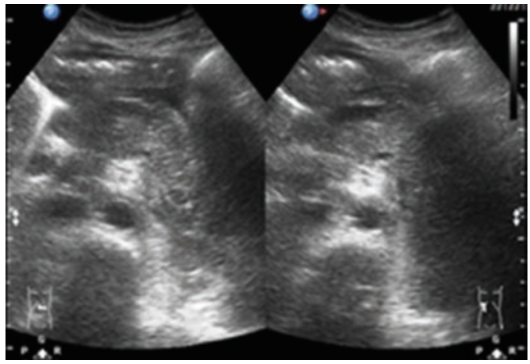

Fig. 3.12 A bulky and inhomogeneous pancreas with presence of peripancreatic fluid in keeping with acute pancreatitis in 8 weeks of pregnancy (Reproduced from [248] under the CC BY 3.0)

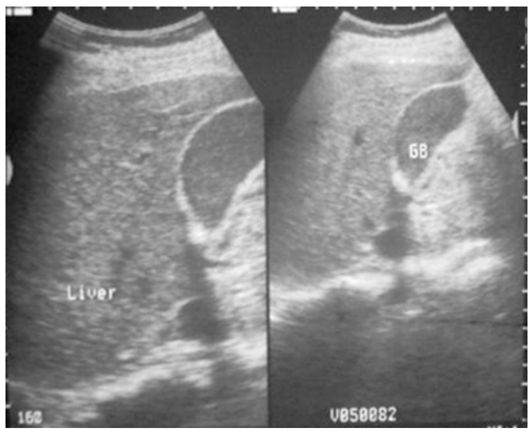

Fig. 3.13 Transabdominal ultrasound showing gallbladder sludge in a 23-year-old nulliparous woman at 33 weeks of pregnancy. Reproduced with permission from [249]

(Fig. 3.13). However, the sensitivity of US in general population in the detection of CBD stones is 20–38% [246, 247]. The US is limited by operator skill, patient obesity, and bowel dilation especially found in patients with peritonitis. However, it is good for focal accumulations larger than 2–3 cm and pancreatic pseudocysts – 54% of the pseudocysts were diagnosed with US (Fig. 3.14).

Additional US role is an estimation of fetal growth and development (length of femur) and fetal vitality by measuring indirect parameters, such as oligohydramnios (Fig. 3.15).

Fig. 3.14 Sagittal section on transabdominal ultrasound demonstrating both smaller (*PC*) and larger pseudocysts. Splenic vein (*Sp.V*) in cross section. Reproduced with permission from [54]

Fig. 3.15 Sonography of the same patient as in Fig. 3.13 showing femur length of 61.4 mm corresponding to 33 weeks of gestation with oligohydramnios. Reproduced with permission from [249]

3.5.3 Abdominal CT

Abdominal computed tomography (CT) should be avoided, especially during the first trimester, because of radiation exposure to the fetus, but has to be performed when benefits outweighed the risk. Abdominal CT is used not only for the diagnosis but also to provide information about the severity of AP (Figs. 3.16, 3.17, 3.18 and 3.19). In a series of 12 cases of AP in pregnant women with AFLP, imaging techniques (US and CT) were accurate in only 58% [127].

Fig. 3.16 Abdominal CT showing a swelling of the pancreas with the adjacent fluid collection, suggestive of acute pancreatitis (*arrow*). Reproduced with permission from [250]

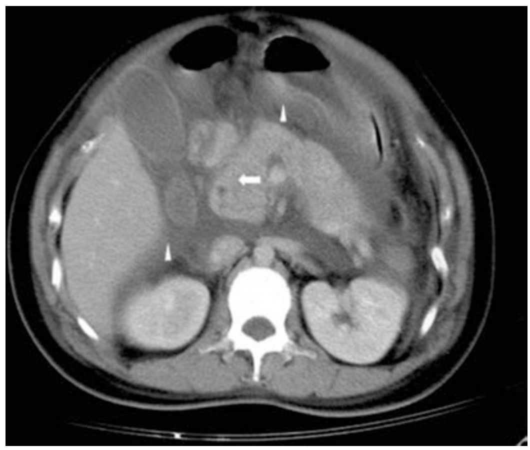

Fig. 3.17 Abdominal CT of a 28-year-old female in the 34th week of pregnancy with swelling of the pancreas and blurring of the mesenteric fat plane (*arrow*). Reactive paralytic ileus, fluid accumulation at bilateral anterior pararenal space, lesser sac, and extraperitoneal space are noted (*arrowheads*). Reproduced with permission from [244]

Fig. 3.18 Pregnant uterus (*f* fetus, *dc* Douglas collection). Reproduced with permission from [127]

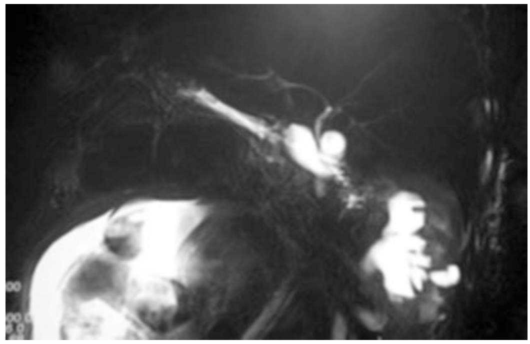

Fig. 3.20 Magnetic resonance cholangiopancreatography showing normal common bile duct and pregnancy in coronal section. Reproduced with permission from [256]

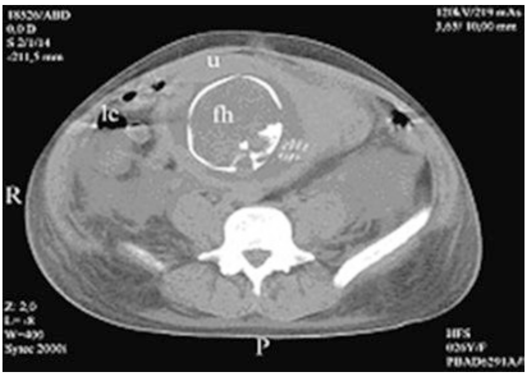

Fig. 3.19 Pregnant uterus (*u* uterus, *fh* fetal head, *lc* liquid collection). Reproduced with permission from [127]

3.5.4 Endoscopic Ultrasound

See Sect. 2.2.5.5.

3.5.5 Abdominal MRI and MRCP

Magnetic resonance imaging (MRI) is indicated in pregnancy if other nonionizing forms of diagnostic imaging studies are inadequate or if the examination provides information that would otherwise require exposure to ionizing radiation with excellent soft tissue contrast (Fig. 3.20). There are some concerns about the safety of MRCP in the first trimester because radiofrequency pulses result in energy deposition and could potentially result in tissue heating [251]. Recent refinements in the technique and the development of 3D MRCP sequences allowed the reconstruction of overlapping slices of less than 1 mm [252, 253]. With a reported accuracy close to 100% in determining the presence and level of biliary obstruction, in general population, MRCP has replaced diagnostic ERCP which diagnostic use steadily decreased from 1996 to 2002 [254, 255].

There are several advantages to using MRCP in the evaluation of pregnant patients who have suspected biliary disease. First, MRCP has high sensitivity and specificity for choledocholithiasis and other common forms of bile duct pathology. Second, MRCP is able to demonstrate the correct cause of biliary dilatation, leading to the identification of a subset of patients who require immediate treatment. The ability of MRCP to provide an accurate evaluation of the entire biliary system allowed the detection of some rare and complex pathologies, such as intrahepatic biliary stones, Mirizzi syndrome and choledochal cyst (see Sect. 2.3). MRCP also obviates the need for intraoperative cholangiography. The third advantage of MRCP is its ability to evaluate the entire pancreas and abdomen for AP and fluid collections [257] and can define pancreatic pseudocysts contrast (Fig. 3.21).

3.5.6 Endoscopic Retrograde Cholangiopancreatography

See Sect 2.2.5.4.

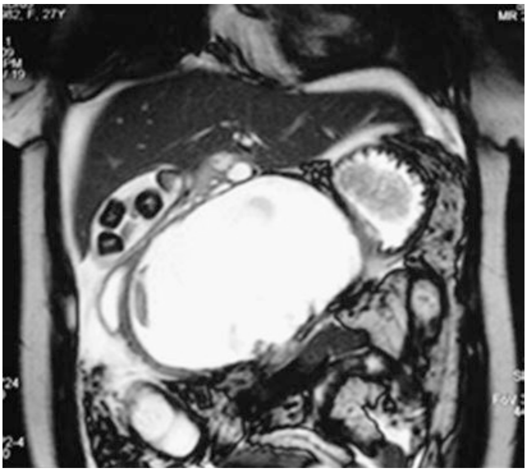

Fig. 3.21 MRCP showing 14 × 7 cm pancreatic pseudocyst in relation to the body of the pancreas, adherent to the posterior wall of the stomach with necrotic debris and gallstones. Gallbladder calculi are seen. Reproduced with permission from [258]

3.5.7 Pancreatic Cyst Fluid Analysis

Cyst fluid analysis can be utilized to differentiate pancreatic cystic neoplasms. In general population, amylase concentration below 250 U/L can effectively rule out pseudocyst [259]. In addition, cyst fluid CA 19–9 level greater than 50,000 U/mL have a sensitivity of 75% and a specificity of 90% for distinguishing mucinous tumors from other cystic lesions [260]. Furthermore, cyst fluid CEA greater than 800 ng/mL has a sensitivity of 42.9% and a specificity of 95.2% for diagnosing pancreatic MCNs [261]. When performing cyst aspiration, however, care must be taken to avoid spillage of cyst contents, which may result in the development of pseudomyxoma peritonei [94], and to avoid uterine perforation, bleeding, or fetal injury.

3.5.8 Imaging of the Parathyroid Glands

In patients with the laboratory findings conclusive of PHPT, imaging should follow to determine both the etiology and location of the causative factor. In general population, mediastinal ectopic parathyroid glands in PHPT have been as high as 20% [262]. The gold standard for imaging in general population is a technetium-99m sestamibi scan. Technetium-99m sestamibi SPECT scanning with the gamma probe can help in intraoperative localization [263]. However, this is contraindicated in pregnancy, and ultrasonography is the preferred imaging modality with 69% sensitivity and a 94% specificity in diagnosing parathyroid adenoma [232]. Parathyroid glands larger than 1.5 cm are typically seen in CT scans, but smaller glands may be difficult to identify. Compared with CT, the sensitivity of MRI was higher for detecting mediastinal lesions but not as good as technetium-99m sestamibi scan alone [264].

3.6 Differential Diagnosis

3.6.1 Acute Pancreatitis per se

Differential diagnosis contains the same diseases present in a nonpregnant population with the addition of some specific diseases found during pregnancy. This is due to the fact that structures containing epithelium of Müllerian and mesonephric duct origin could produce amylase [265]. This includes the pancreas, salivary glands, Fallopian tubes and ovarian cyst fluids, testes, thyroid, tonsils, breast milk, sweat, tears, and some malignant neoplasms [266]. Therefore, hyperamylasemia has been reported to occur with perforated peptic ulcer, perforated appendicitis, intestinal obstruction, mesenteric infarction, pulmonary embolism, pneumonia, myocardial infarction, lymphoma, hyperemesis gravidarum [267–269], and several tubo-ovarian pathologies, including ruptured ectopic pregnancy, salpingitis, pelvic inflammatory disease, ovarian papillary serous cystadenocarcinoma, ovarian adenosquamous carcinoma, ovarian endometrioid carcinoma, mucinous tumors, and surface papillary carcinoma [252, 253]. In all published cases of hyperamylasemia associated with tubo-ovarian disease in which isoenzyme analysis was performed, the predominant amylase has been shown to be either electrophoretically identical to s-type amylase or an acidic

variant thereof [270]. However, predominantly p-type hyperamylasemia has up to this case been reported previously with tubo-ovarian disorders. In addition, hemolysis of extravasated blood might have been the reason of the elevated pancreatic enzyme activity [271]. The problem is if, wrongly, hemorrhagic AP is suspected and conservative approach indicated, prolonged hemorrhage from ruptured ectopic pregnancy can lead to hemorrhagic shock [272].

In terms of diagnostic accuracy, lipase has been proven to be superior to amylase in AP [217]. However, lipase is also not specific to the pancreas, having been isolated in the tongue, esophagus, stomach, duodenum, small bowel, liver, lung, and adipose tissue [269]. Consequently, hyperlipasemia has been reported to appear in the event of cholecystitis, esophagitis, peptic ulcer disease, enteritis, peritonitis, and bowel obstruction and infarction [218, 269].

3.6.2 Hypercalcemia

The most common cause of hypercalcemic AP in pregnancy is PHPT, but there are many causes of hypercalcemia (Table 3.3). However, if lytic bone lesions in the presence of hypercalcemia are evident, the differential diagnosis narrows to include bone fat necrosis secondary to AP, metastatic cancer (primary source uncertain), multiple myeloma [273], Paget disease (osteodystrophia deformans), primary lymphoma of the bone, leukemia, and rhabdomyosarcoma.

3.7 Treatment

When a diagnosis of AP in pregnancy is made, assessment of severity based on clinical signs, blood tests, urinalysis, and imaging tests should be performed to determine the appropriate treatment for each patient. The treatment of AP is not standardized and is mainly supportive, and severe AP is still a significant clinical problem for all physicians. The treatment goals are to avoid organ failure and infectious complications which also influence the fetal development. With the advances in diagnostic techniques and therapeutic methods, maternal and fetal outcomes have significantly improved over the last decades.

3.7.1 Conservative Treatment

3.7.1.1 Supportive Measures

Treatment should include (1) the treatment of the AP itself and (2) specific treatment/elimination of the cause of AP. The initial management of AP during pregnancy is similar to management in nonpregnant patients. It consists of fluid restoration, oxygen, analgesics, antiemetics, and monitoring of vital signs. An adequate volume of intravenous fluid should be administered promptly to correct the volume deficit and maintain basal fluid requirement [274–276]. Fluid resuscitation should be done carefully by closely monitoring the patient's vital signs. Important additional measures during pregnancy include fetal monitoring, attention to the choice of medications, and positioning of the mother to avoid inferior vena cava obstruction. Mild AP (MAP) treated conservatively usually resolves within 7 days. Ten percent of patients have severe course, and they are best managed in an intensive care unit (ICU) (see Sect. 3.7.1.4).

Parenteral nutrition is considered to be safe and necessary in pregnancy [23]. There are still different opinions on the use of total parenteral nutrition (TPN) or enteral nutrition (EN). EN in SAP is better than TPN, in patients without nausea and vomiting, because EN may help to maintain the immune function of the gastrointestinal mucosa, protect the mucosal barrier, and improve the blood supply to the small intestine [274].

Many pharmacological agents (somatostatin, octreotide, N-acetylcysteine, gabexate mesylate, lexipafant, and probiotics) have been investigated in AP, but because most of them have failed to show a positive effect, these should be avoided in pregnancy. The use of somatostatin may be effective to improve pathophysiology of the pancreas, especially in the early stage of AP. Applying somatostatin to inhibit both exocrine and endocrine portions of the pancreas is a very important part of nonsurgical treatment. However, it has not

yet been proved whether somatostatin should be applied in pregnancy because of its potential effect on the fetus. Somatostatin administered in ten cases confirmed good outcomes without malformations and abnormal newborn [104]. Treatment strategy cases with SAP are as follows: when the benefits of the drug may outweigh its risks with the permission of the patient and the agreement and signing of her family member, somatostatin is used in the early stage of SAP. Somatostatin should be infused continuously with intravenous syringe infusion pumps with a low dose (150–250 μg/h) for 24–72 h and then reduced or withdrawn timely when the condition improves with hemodynamic stabilization. Despite the encouraging results, somatostatin is not recommended for routine use. Cessation of oral feeding has been thought to suppress the exocrine function of the pancreas and to prevent further pancreatic autodigestion. Bowel rest is associated with increased infectious complications, and TPN and EN have an important role in the management of AP. TPN has been for years a traditional treatment of AP but carries a significant risk of infections and metabolic distress. EN is physiological, helps the gut flora maintain the gut mucosal immunity, and reduced translocation of bacteria while simultaneously avoiding all the risks of TPN. Parenteral nutrition in pregnancy is considered safe and necessary when adequate oral nutrition is not possible, although the frequency of complications from centrally inserted catheters is higher than in nonpregnant patients [277]. MAP does not require nutritional support, as the clinical course is usually uncomplicated and a low-fat diet can be started within 3–5 days. Treatment of SAP should include EN by nasojejunal tube and, if needed, should be supplemented by parenteral nutrition [278].

3.7.1.2 Antibiotics

Prophylactic use of antibiotics is controversial and the choice of antibiotic in pregnancy is difficult. Antibiotics have no role in the treatment of MAP, normal CBD size, and no evidence for cholangitis, while broad-spectrum antibiotics in the treatment of CT-proven necrotizing SAP could be beneficial [274–276]. The available evidence demonstrates that antibiotic prophylaxis might have a protective effect against non-pancreatic infections but failed to show a benefit on the reduction of mortality, infected necrosis, and need for surgical intervention [279]. Due to the lack of evidence on the beneficial effect of antibiotics, an even more conservative approach is recommended in pregnancy. Regardless of the initial drug regimen, therapy should be modified to reflect the organisms recovered in blood cultures and the clinical status of the patient.

In a meta-analysis of the general population, only *imipenem* significantly reduced the risk of pancreatic infection [279]. The use of imipenem/cilastatin is indicated in necrotizing AP, but dose adjustment in pregnancy (FDA category C) should be considered even though there are currently no studies proposing the optimal dose [280]. The pharmacokinetics of imipenem will change during pregnancy with a larger volume of distribution and faster total clearance from plasma [281]. *Metronidazole* passes freely across the placenta, but there is not an increased risk of teratogenic effects [282]. *Quinolones* (FDA category C) are alternative to first-line antibiotic therapy.

3.7.1.3 Continuous Renal Replacement Therapy

Continuous renal replacement therapy (CRRT), including a variety of blood purification techniques, which can remove water, nitrogenous wastes, and even inflammatory mediators, slowly and steadily, has been widely used in patients with critical conditions such as severe AP. CRRT is associated with significant improvement in pulmonary gas exchange, hemodynamic instability, azotemia control, fluid overload, and nutritional support in patients with MODS and acute renal failure [283]. Different modalities of continuous venovenous hemofiltration (CVVH) can prevent sepsis and improve survival in AP [284]. However, CVVH does not allow large molecules to pass through the hemofilter. Ronco et al. proposed a *peak concentration hypothesis* of MODS and found that CVVH can be combined with plasma filtration absorption tech-

niques to remove the excess circulating inflammatory mediators [285]. Hemoperfusion (HP) is another blood purification modality which can absorb pathogenic molecules in the blood flow circuit by sorbent materials installed in the hemoperfusion cartridge. Unlike CVVH, HP is more effective for removing middle and large molecules and toxins bound to proteins. This treatment can effectively reduce the serum levels of proinflammatory cytokines during severe AP and improvement of PaO2/FiO2. In the only pregnant patient with AP, authors combined CVVH and broad-spectrum HP, assuming that HP can effectively remove excess endogenous and exogenous pathogenic molecules. After the first 3 days of treatment, the patient's general condition significantly improved and laboratory parameters virtually normalized [286]. After receiving HP and CVVH treatments, the TG, CHOL, amylase, and lipase levels decreased dramatically (Fig. 3.22), explaining rapid recovery [286]. Moreover, the patient developed no side effects such as coagulopathy, hypotension, thrombocytopenia, or hypocalcemia.

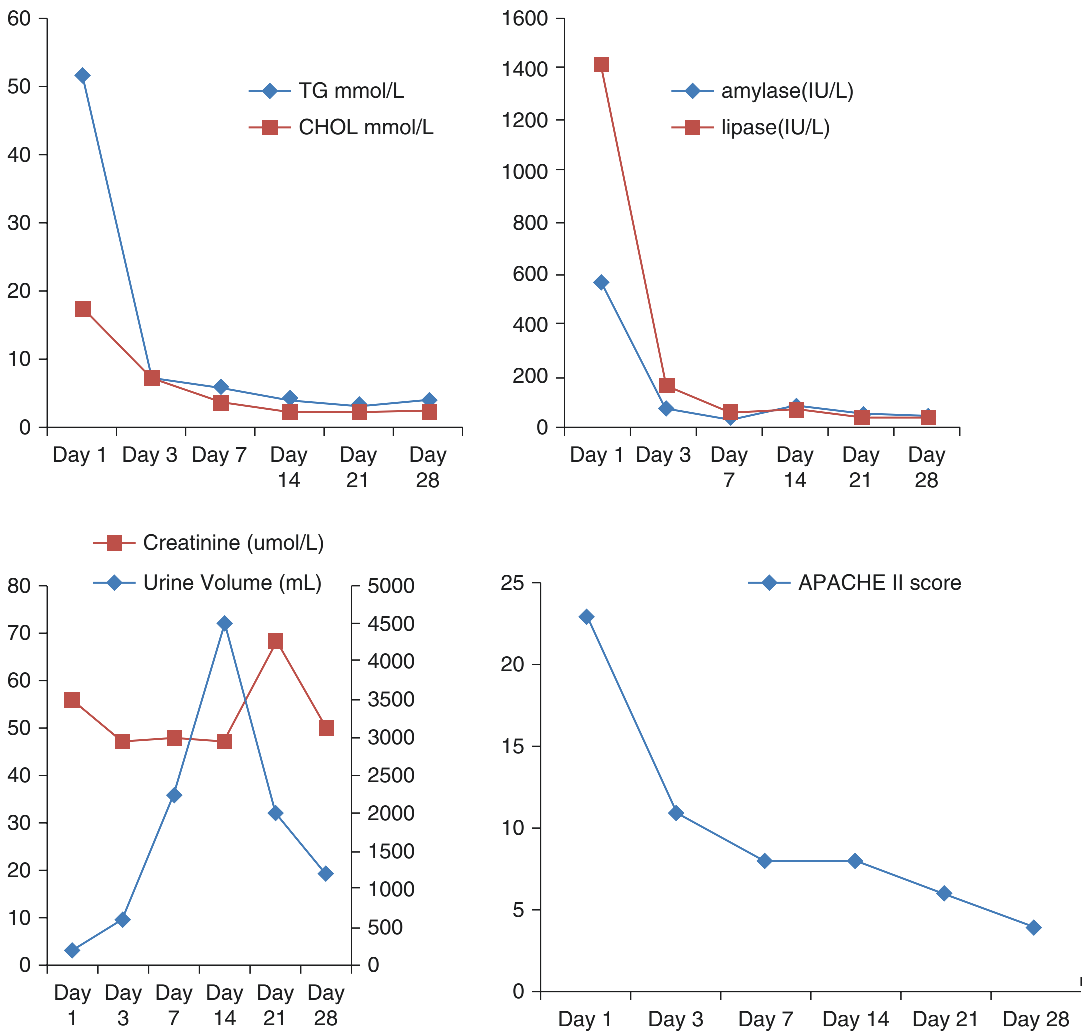

Fig. 3.22 The changing tendency of triglyceride (*TG*), cholesterol (*CHOL*), amylase, lipase, renal function, and APACHE II score during the treatment. CVVH and HP were initiated on day 1 and discontinued HP on day 3. CVVH was stopped on day 7. Normal range: TG 0.29–1.83 mmol/L, CHOL 2.8–5.7 mmol/L, amylase 25–125 IU/L, lipase 13–60 IU/L. Reproduced with permission from [286]

3.7.1.4 Intensive Care Unit

In the general population, indicators for admission to ICU are [287]

- Need for fluid resuscitation
- BMI >30 kg/m^2
- Pleural effusions
- CRP >150 mg/L at 48 h
- Necrosis of over 30% of the pancreas
- Ranson criteria ≥3

The third-space fluid sequestration is the most serious hemodynamic disorder leading to hypovolemia and organ hypoperfusion resulting in multiple organ failure. In volume-depleted patients, the essential treatment modality is initial electrolyte infusion of 500–1000 mL/h [288]. Monitoring of hydration, cardiovascular, renal, and respiratory functions is important for early detection of volume overload and electrolyte disturbances. Organ failure may occur in 50% of patients. Early admission and management of critically ill obstetric patients in the ICU decrease maternal mortality and morbidity [289].

3.7.1.5 Hyperlipidemic Pancreatitis

The goals of management of pregnant patients with HTG-induced AP should include decreasing the serum TG concentration and pancreatic activity while supplying maternal and fetal nutritional needs. Preconceptional control of TG levels may prevent or shorten the course of AP.

Lipid-Lowering Diet

There is no consensus on the threshold of triglycerides for intervention in pregnancy, although 5.6 mmol/L has been suggested. When the etiology is LPL deficiency, pharmacological therapy is relatively ineffective. In this setting, the role of dietary restriction is central. The prepregnancy patient should work closely with the dietician and focus on a low-fat diet. Strict adherence to a low-fat diet, usually ≤20 g/day and sometimes as low as ≤10 g/day, cuts off the production of chylomicrons [290] and decrease serum TG concentration (Figs. 3.23

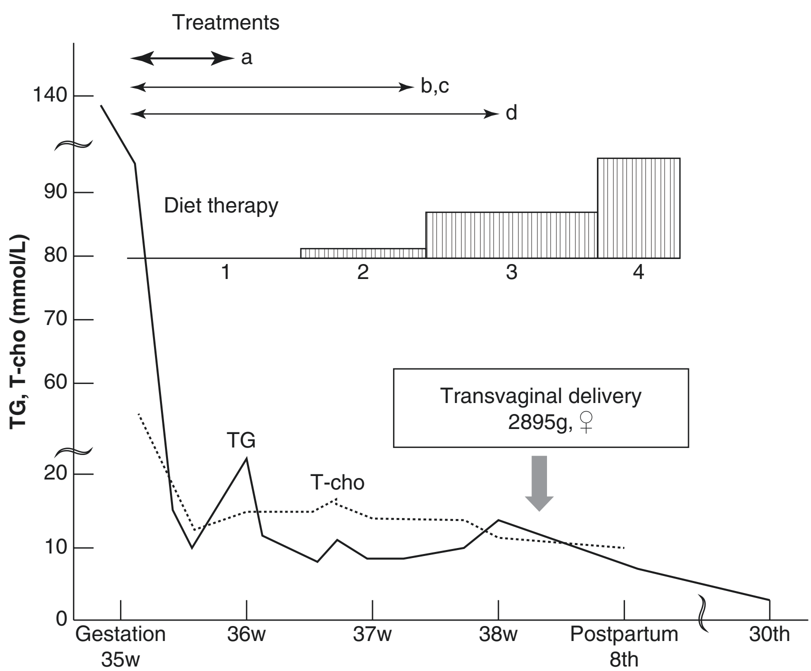

Fig. 3.23 The first pregnancy with type V hyperlipidemia complicated with AP. Treatments were dietary therapy ((*1*) fasting for 11 d, (*2*) fat-restricted diet including 2.0 g of fat for 6 d, (*3*) fat-restricted diet including 10.0 g of fat, and (*4*) fat-restricted diet including 20.0 g of fat) and (*A*) a protease inhibitor (ulinastatin), (*B*) antibiotics (piperacillin, sulbactam/cefoperazone), (*C*) H$_2$-blocker (famotidine), and (*D*) anticoagulation therapy (heparin) from admission. *T-cho* total cholesterol, *TG* triacylglycerol. Reproduced with permission from [292]

and 3.24). However, it paradoxically increases the synthesis of VLDL which leads to enhanced production of TGs by the liver elevating the serum TG levels [291]. Total caloric intake should be adequate, and what little fat is ingested should contain ω-3 and ω-6 fatty acids [292]. Medium-chain TG-rich foods, such as coconut oil, can be used for cooking, as they are absorbed directly into the portal vein without becoming incorporated into the chylomicron TG. The growing fetus requires essential fatty acids and amino acids for development and maturity of vital organs like the brain and lungs. The concern is that a very low-fat diet might lead to a deficiency in essential fatty acids, hence having an adverse effect on fetal development, but this is not confirmed.

Antioxidant therapy has been used in the management of HTG in patients with recurrent AP due to familial LPL deficiency [293]. The antioxidant cocktail (α-tocopherol, β-carotene, vitamin C, organic selenium, and methionine) significantly reduces the recurrence of AP and could safely be administered during pregnancy. Antioxidants neutralize free radicals resulting from chylomicronemia-related microvascular ischemia and thereby prevent the potential damage to pancreatic acinar cells and the resulting AP. Alcohol, oral estrogen therapy, or selective estrogen receptor modulators such as tamoxifen or raloxifene should be discontinued.

Total Parenteral Nutrition

A favorable effect of intravenous hyperalimentation with nothing by mouth for HTG-induced AP in pregnancy was first referred by Weinberg et al. in 1982 [293]. Avoidance of oral diet and intravenous administration of 5% dextrose along with insulin (see next section) often lead to a dramatic reduction of serum TGs [294, 295]. However, intravenous 5% dextrose does not supply enough calories and could not be used for the extended duration required for enteric rest. TPN is an effective means of providing the necessary calories and essential amino acids for the growing fetus while controlling the maternal TG concentrations and preventing the induction of AP. TPN with up to 10% of calories of fat does not significantly increase maternal serum TG. This is because of the systemic delivery of lipids which bypasses the liver where production of TG-rich lipoproteins occurs. It also enables the supply of other nutritional supplements that are required by the fetus. Parenteral nutrition in pregnancy should be managed preferably by an experienced clinical nutrition support staff.

The major complications are related to central venous catheter placement and include pneumothorax, hemorrhage, and rarely death [296]. There has been a trend toward the use of peripherally inserted central catheters (PICC) because of a lower rate of major complications and relative ease of insertion compared to central venous

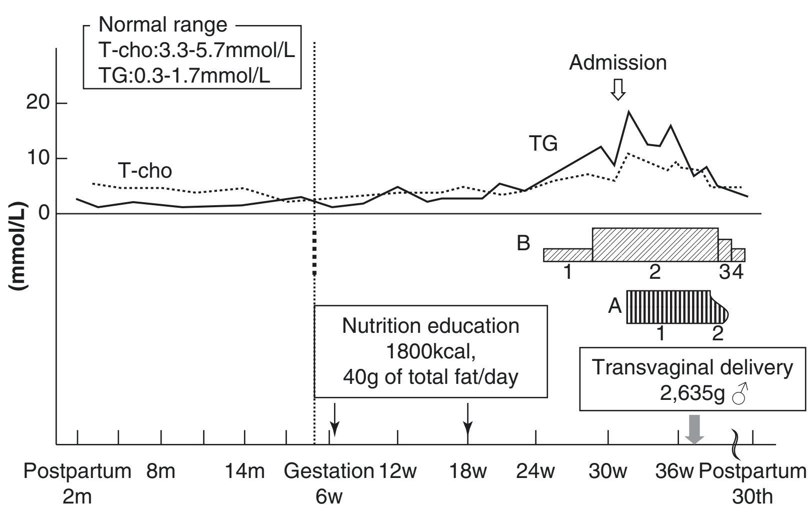

Fig. 3.24 The second pregnancy with type V hyperlipidemia of the same patient without AP. Treatments were (*A*) dietary therapy ((*1*) fat-restricted diet including 20 g of fat daily, (*2*) fat-restricted diet including 15 g of fat daily) and (*B*) ω-3 fatty acids ((*1*) 0.9 g, (*2*) 2.7 g, (*3*) 1.8 g, (*4*) 0.9 g). *T-cho* total cholesterol, *TG* triacylglycerol. Reproduced with permission from [292]

catheters [296]. PICCs should always be considered particularly in high-risk populations like pregnant women. However, there is a higher rate of minor complications like thrombophlebitis [277]. PICC insertion is highly operator dependent, and lowest complication rates have been seen in the most experienced centers [297].

L-Thyroxine

Hypothyroidism has a well-established association with hyperlipidemia. In general population, hypothyroidism is present in 1.4–13% of patients with hyperlipidemia [168] with elevated TG levels in up to 35% of hypothyroid patients [167]. A low circulating free thyroid hormone level may impair LPL activity in adipose tissue. Impaired LDL receptor activity may result in decreased clearance and thus an accumulation of LDL particles. Replacement therapy with L-thyroxine may reverse both of these defects. In the general population, approximately 50% of those with elevated TSH levels were treated with levothyroxine; 30% of patients with TSH levels greater than 10 mIU/L were not treated. Among patients who received levothyroxine, a considerable proportion (75%) did not require a lipid-lowering agent within 1 year [298]. If this therapy fails, lipid-lowering medications or plasma exchange has been used [229, 299]. In addition, in hypothyroidism, glucose uptake in muscle and adipose tissue is resistant to insulin. The decrease of blood flow in adipose tissue and muscle may be considered as part of the pathogenetic mechanism of insulin resistance explaining most of the metabolic defects in these tissues [297]. Therefore, it could be recommended to confirm hypothyroidism in insulin-dependent diabetic patients because of the synergistic therapeutic effect of L-thyroxine and insulin.

Insulin

Insulin activates LPL, an enzyme that accelerates chylomicron degradation into glycerol and FFAs [300]. It also increases its synthesis [139]. Successful management with insulin monotherapy in the setting of HTG-induced AP has been demonstrated [229]. Insulin (with the administration of glucose) is safe and effective in the treatment of HTG-induced AP, even in patients without DM [229]. Intravenous insulin may be more effective than subcutaneous insulin in severe cases given the potential limitations of absorption with the subcutaneous route. Intravenous insulin may be given as a continuous infusion starting with 0.1–0.3 U/kg/h with titration as required.

Heparin

LPL is a ubiquitous, endothelially bound lipolytic enzyme. Intravenous heparin uncouples the enzyme from its endothelial anchor, thus stimulating the release of endothelial LPL into the circulation [301]. This postheparin lipolytic activity includes predominantly hepatic TG lipase and LPL as well as other lipases such as monoglyceride hydrolase and phospholipase, which have lesser hydrolytic activities against a TG substrate. It has been used without insulin to successfully lower HTG [299, 302]. A heparin dose of 10,000 U/day seems to be therapeutic and safe, as evidenced by a normal APTT [43, 299]. Despite the success of intravenous heparin in combination with insulin in HTG management, heparin has come under greater scrutiny. Intravenous heparin does cause an initial rise in circulating LPL levels but is quickly followed by increased hepatic degradation [303]. This degradation contributes to further depletion in plasma stores of LPL and may ultimately potentiate the subsequent accumulation of circulating chylomicrons [304]. Another potential hazard is the risk of transformation into hemorrhagic AP with worsening of the ultimate outcome.

Plasmapheresis

Plasma apheresis for severe HTG in general population was first reported in 1978 [305]. In clinical practice, plasmapheresis or lipid apheresis is indicated with [306]:

- Unsuccessful nutritional, lipid-lowering agents or heparin/insulin therapy
- Serum triglycerides >1000 mg/dL
- Serum lipase is 3× the upper limit of normal
- Hypocalcemia
- Lactic acidosis
- Worsening inflammation and organ dysfunction

Prophylactic plasmapheresis has been proposed as a preventive treatment for severe uncontrolled HTG. There is a reduced incidence of HTG-induced AP in such patients at 4-week intervals [307]. In one study, 18.1% patients with HTG-induced AP in pregnancy underwent plasmapheresis with no maternal and fetal complications. TG levels usually rapidly decrease after several sessions of plasmapheresis [41] approximately by 50% after the second session, depending also on the initial values of TG (Fig. 3.25) [41, 308, 309]. Crystalloid solution and albumin are used for plasma exchange with a volume of 40 mL/kg along with heparin infusion 10 U/kg/h for anticoagulation.

Plasmapheresis is successful in lowering TG and serum pancreatic enzyme levels [308]. However, in the absence of a comparison with standard treatment (heparin or insulin infusion and lipid-lowering agents), the effect of plasmapheresis on lowering the morbidity and length of stay of patients with HTG-induced SAP is uncertain and warrants further investigation. Another problem is the small number of patients for making strong conclusions. After successful plasmapheresis, treatment modalities include dietary intervention, followed by pharmacological therapy that includes fibric acid derivatives, ω-3 fatty acids, and nicotinic acid derivatives, insulin, and/or heparin treatment.

The double-filtration technique presents major advantages compared to standard plasma exchange [310]. The first filter is a polyvinyl alcohol hollow fiber membrane, providing pores of 0.2 μm diameter in which plasma is separated at first and then introduced into a second filter with smaller pore size. This second filter is an ethylene-vinyl-alcohol copolymer membrane, discarding only large weight molecules such as lipoproteins, whereas albumin, IgG, and coagulation proteins are returned to the patient along with the whole bloodstream. The loss of low-molecular-weight molecules such as albumin is reduced, therefore decreasing the amount of required substitution fluid. In addition, IgG and coagulation proteins are saved, thus reducing the major risks of plasma exchange, namely, infections and bleeding.

Some authors indicated plasmapheresis as the first treatment with the successful lowering of TG and disappearance of AP symptoms [310]. In addition, this eliminates the need for insulin and heparin therapy because it provides normalization of serum glucose levels.

First reports of long-term extracorporeal elimination of TG-rich lipoproteins by three modes of treatment (plasma exchange, immunospecific apheresis, and a combination of both treatments) were by Swoboda et al. [311, 312]. The loss of immunoglobulins remained acceptable.

Heparin-induced extracorporeal low-density lipoprotein (LDL) precipitation therapy selectively removes LDL cholesterol, fibrinogen, and other lipoproteins from the plasma. It is indicated

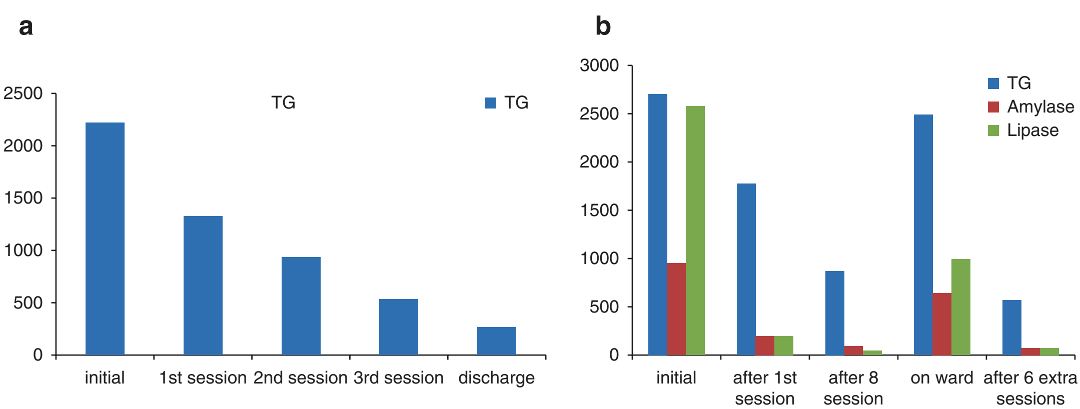

Fig. 3.25 (**a**, **b**) The change of lipid profile with plasmapheresis therapies. *TG* triglyceride. Reproduced with permission from [309]

for lipid management of familial lipidemias or preeclampsia in pregnancy due to beneficial effects of (1) lowering of plasma CRP, (2) increased production of nitric oxide leading to endothelial function improvement, (3) decreased atherogenic LDL oxidation, and (4) inhibition of expression of endothelial-derived leukocyte adhesion molecules and vascular cell adhesion molecules. Probably the benefit of this procedure is questionable in HTG AP because there is no influence on lowering serum TG levels which cause AP.

Lipid-Lowering Medications

It should be noted that therapies like plasma exchange, use of lipid-lowering medications, and extracorporeal lipid elimination may be effective in controlling triglyceridemia with or without resulting AP but do not meet the nutritional requirements of the mother and child [311, 313].

Fibrates

Fibrates (fibric acid derivatives) include bezafibrate, ciprofibrate, clofibrate, fenofibrate, and gemfibrozil. Fibrates effectively lower TG levels by 40–60% and raise HDL-C levels [314]. The TG-lowering effects of fibrates have been attributed to enhanced catabolism of TG-rich particles and reduced secretion of VLDL [314]. Nicotinic acid lowers TG levels by 30–50% by reducing VLDL secretion, but flushing and gastric upset are prominent side effects [156]. Ω-3 fatty acids have proved capable of lowering high TGs (5.5–22.5 mmol/L, 500–2000 mg/dL) by 45% [315]. Fenofibrate 200 mg and niacin 500 mg daily and ω-3 fatty acids are relatively ineffective in patients with primary (genetic) HTG. All fibric acid derivatives are renally excreted and can consequently display a prolonged plasma half-life of several days in severe renal impairment cases. Since all fibric acid derivatives have a high degree of protein binding (>95%), none are removed by hemodialysis [316]. Gemfibrozil is the most frequently prescribed lipid-lowering agent for patients with renal insufficiency, as it is least dependent on renal excretion [317]. Gemfibrozil has however been reported to cause rhabdomyolysis in patients with compromised renal function. Although most incidences of rhabdomyolysis occur in patients taking both gemfibrozil and HMG-CoA reductase inhibitor [318], rhabdomyolysis induced by gemfibrozil alone has also been reported [319]. The pathophysiologic mechanism of gemfibrozil toxicity remains unknown, despite its relatively frequent occurrence.

Despite legitimate safety concerns regarding the use of fibrates, nicotinic acid, and ω-3 fatty acids in pregnancy, case reports of patients being prescribed these drugs suggest that they may be safe for both the mother and the fetus [320].

Statins

Epidemiological data suggest that statins are not major teratogens but are currently contraindicated in pregnancy (FDA category X). The percentages of normal outcomes (85%), congenital abnormalities (4%), spontaneous abortions (8%), fetal deaths/still births (1%), and miscellaneous adverse outcomes (2%) are not higher than those expected in the general population [321, 322]. The actual risk for an exposed pregnancy seems to be small, if present at all, and does not by itself warrant termination of pregnancy. Nevertheless, it is still advisable to avoid the use of these drugs in patients who are planning pregnancy in order to reduce the risks [323]. There are also cases of statin-induced AP in general population (see Sect. 3.3). There are no recommendations for hyperlipidemic AP in pregnancy where benefits could outweigh the risks including short duration of statin therapy.

3.7.1.6 Primary Hyperparathyroidism

Medical therapy in pregnancy for symptomatic PHPT has been discouraged, due to safety issues of drug therapy and the suboptimal control of serum calcium which leads to a high fetal loss rate [67]. However, some groups of patients diagnosed in the third trimester may be managed medically, postponing the operation until after delivery:

- Symptom-free patients
- No radiologically identifiable parathyroid adenoma
- Mild hypercalcemia
- Significant hypercalcemia who are not surgical candidates

Medical therapy primarily involves stabilizing the patient with hydration, limiting calcium intake, and correcting electrolyte imbalance. Early treatment of urinary tract infections and avoiding medications known to cause elevations in serum calcium such as vitamin D, vitamin A, aminophylline, and thiazide diuretics are important therapeutic measures. Serum calcium should be determined on a regular basis.

High-dose *magnesium sulfate infusion* might be a therapeutic alternative for PHPT in pregnancy [69, 82, 87]. It is possible that a compensatory increase in serum vitamin D-1,25 in response to the decrease in the PTH level caused by the magnesium increased calcium absorption from the gastrointestinal tract. Therefore, for some patients, because of persistent hypercalcemia, magnesium sulfate might not be a viable treatment option for PHPT during pregnancy [69].

When magnesium proves ineffective, other agents such as phosphate-of-soda enemas, oral phosphates phosphate (inorganic phosphorus in doses of 1.5–2.5 g/day), and loop diuretics have been used with varied success [60, 68, 82, 105]. Side effects of *oral phosphate* therapy include nausea, vomiting, and hypokalemia. These problems can be easily avoided by decreasing the dose of medication.

If the patient with the indication for operative treatment chooses medical therapy for PHPT, *calcitonin* is administered. It is considered the safest conservative treatment option in patients with hypercalcemia in pregnancy [67]. The safety probably results from its negligible passage through the placenta [105, 324]. The choice of this agent was also supported by suggested but not fully supported beneficial effects of calcitonin in the management of AP observed in nonpregnant patients. In order to limit the risk of serious complications, most recommend maintaining total plasma calcium <3.0 mmol/L [325]. Exceeding this level is considered an indication for calcitonin administration. Interestingly, although calcitonin treatment may be associated with the development of tachyphylaxis [326], the only tendency to tachyphylaxis was observed in the third trimester, and it disappeared after the introduction of oral phosphates. This fact may be explained by administration of this agent only if plasma calcium levels exceeded the established threshold. Moreover, there was no nausea, vomiting, diarrhea, flushing, injection site reactions, and any other side effects associated with calcitonin treatment [326]. Interestingly, the benefits of combined administration of calcitonin and cinacalcet in pregnancy and puerperium have been shown [325]. The presence of transient mild hypocalcemia probably resulted from increased calcium levels in fetal plasma, inhibiting parathyroid PTH synthesis and release during the pregnancy [105, 324]. Interestingly, neonatal hypocalcemia was absent in the patient's subsequent pregnancy, taking place after parathyroidectomy, which supports the recommendations that surgery should be considered the treatment of choice in young PHPT pregnant women or desiring pregnancy [73, 194].

In the past *mithramycin* was used but is currently contraindicated secondary to teratogenic effects [77].

Corticosteroids have also been used to decrease the absorption by the gastrointestinal tract but have shown a minimal effect when the hypercalcemia is secondary to PHPT [77].

3.7.1.7 Acute Fatty Liver of Pregnancy

The treatment for AFLP is predominantly supportive. Patients with encephalopathy may require intubation and mechanical ventilation. Profound coagulopathy may necessitate the transfusion of blood products for correction and stabilization. Close monitoring of renal function and fluid status is of the utmost importance. Invasive hemodynamic monitoring may be necessary for some patients to assess fully the intravascular volumes and maintain renal perfusion.

> The resolution of the disease is heralded by the initial improvement of hepatic dysfunction. Liver enzymes, ammonia, cholesterol, and coagulation begin to normalize and is followed by a decrease in serum creatinine, as long as permanent damage to the renal parenchyma has not occurred. Once these measurements show improvement, serum amylase and lipase typically will normalize [127].

3.7.2 Surgical Treatment

Surgical treatment has two aspects, which include operative intervention for the AP itself and surgical management of associated local (biliary tract disease, pancreatic tumor) or distant (PHPT, HTG, etc.) cause of the AP during an attack or once the acute inflammation subsides.

Early surgery for necrotizing AP is not recommended, and it should be delayed as long as possible [21]. Remission could be achieved in most patients (78.9%) with the conservative treatment. Therefore, the indications for surgery and antibiotics are [21, 274–276, 287]:

- Pancreatic necrosis and infection (3–4 weeks after the onset of symptoms)
- Large intra-abdominal exudates
- Clinical deterioration

Minimally invasive surgical techniques are getting wider acceptance. Percutaneous drainage, endoscopic drainage, or surgical procedures can be selected in accordance with the conditions of individual cases. The decompression and percutaneous drainage help to avoid or delay surgery in most patients with SAP [21, 276]. For patients with pancreatic abscess, drainage is recommended [275]. Necrosectomy (Fig. 3.26) should be performed as late as possible, and it can be also performed during the CS through median laparotomy.

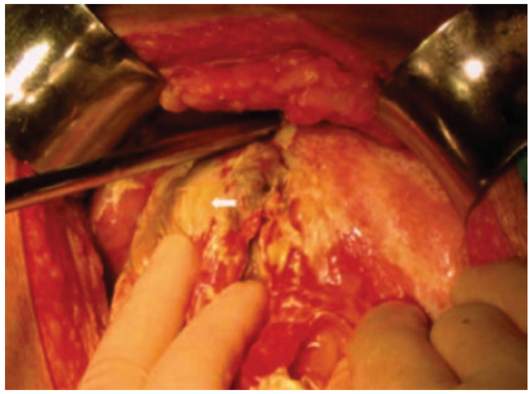

Fig. 3.26 Prominent pus coating over the omentum, intestine, and colon, peripancreatic fatty necrosis, and excessive solid mass of swollen inflamed pancreas. An area of impending perforation (*arrow*) is over the transverse colon. Reproduced with permission from [244]

3.7.2.1 Pancreatic Pseudocysts

Limited information is available to guide the management of pancreatic pseudocysts in pregnancy. Many case reports occurring during pregnancy are limited by the lack of US measurements. In general population, the recommended management is to observe (1) asymptomatic pseudocysts, (2) those present for less than 6 weeks, and (3) pseudocysts less than 5 cm in diameter, as these have a 30–40% rate of spontaneous resolution. Although it is recommended that uncomplicated pseudocysts should be surgically managed in the postpartum period [327, 328], some raised concern that the pseudocyst might rupture because of the decreasing space within the abdominal cavity because of the growing fetus or later during delivery as has been reported [329]. Seventy-six percent were treated postpartum with definitive surgical treatment after a variety of antenatal "holding" maneuvers [54, 330]. When the pseudocyst is infected, located greater than 1 cm from the bowel, or has a cyst wall insufficiently thick to permit anastomosis, percutaneous drainage can be considered despite a recurrence rate of 20–70% [331, 332] and the potential risks of infection and fistulization [332]. An indwelling transgastric or transduodenal pigtail catheter may be placed or a more permanent internal fistula created by cautery between the cyst and the adjacent viscus. This last procedure, while reportedly effective, carries a significant risk of bleeding and depends on the skill of the endoscopist. Endoscopic transpapillary stenting is another alternative for patients with a partial pancreatic duct disruption and a communicating pseudocyst.

Surgical internal drainage is preferred for:

- Symptomatic pseudocysts
- Pseudocysts >5 cm in diameter
- Those present for over 6 weeks

These have a 3% chance of resolution and a 57% risk of rupture, infection, hemorrhage, or obstruction [331]. Internal drainage can be accomplished by anastomosis to the duodenum, a Roux-en-Y limb of the jejunum, or the posterior wall of the stomach.

Table 3.6 compiles the available information about the presentation, etiology, management, and outcomes in these cases since 1980 when the US, amylase, and lipase became widely available [56]. Pancreatic pseudocysts complicate 6.9% of cases of AP and are almost never found in association with gallstone AP in pregnancy. Six of eight women with known gestation were primiparous. Alcohol was the etiology in less than a quarter of the cases. Gallstones, by far the most common cause of AP during pregnancy [11], accounted for only one case.

The natural history of pancreatic pseudocysts appears similar to that in nongravid patients because pseudocysts less than 5 cm shrank or resolved while those greater than 5 cm remained the same size or enlarged. In three cases, the intervention was performed antepartum: two patients underwent percutaneous drainage and one was stented endoscopically. Percutaneous drainage of one 6 cm cyst had an unspecified result [51]; another, of a 13 cm cyst at 24 weeks of gestation, showed initial relief of symptoms and reduction in cyst size with daily aspirations. However, in the latter case, the cyst subsequently collapsed around the drain, the cyst reaccumulated, and the patient had a preterm delivery [332]. One patient had a cystogastric stent placed with ERCP at 17 weeks of gestation. In this case, the cyst shrank from 7 to 2 cm after the stent placement but grew rapidly to 4 cm once the stent fell out. A transpapillary stent was then placed at 35 weeks of gestation, which stabilized the cyst until delivery at term [330].

3.7.2.2 Pancreatic Tumors

Mucinous cystic neoplasms are considered premalignant lesions and resection is recommended. Cystic neoplasms are even less common than pancreatic pseudocysts but can occur during pregnancy and may mimic inflammatory fluid collections. Factors to help differentiate inflammatory from neoplastic fluid collections include serum amylase level, which is elevated in 50–75% of pseudocysts [332] and 5% of pancreatic neoplasms [332]; cyst amylase level, which is normal in neoplasm and elevated in inflammatory fluid collections; ultrasonography demonstrating multiple cysts or internal septa suggesting neoplasm rather than inflammation [332]; and a history of AP or antecedent factors suggesting an inflammatory cause such as gallstones, hyperlipidemia, or alcoholism.

3.7.2.3 Primary Hyperparathyroidism

PHPT in pregnancy represents a significant risk for maternal and fetal complications that cannot be predicted by duration of symptoms or serum calcium levels. Indications for parathyroidectomy regardless of the trimester of pregnancy are [113]:

- Persistent symptoms
- Serum Ca >11 mg/dL
- Acute pancreatitis

In 1947 Petit and Clark carried out the first parathyroidectomy during pregnancy [333]. Successful surgical management of PHPT eliminates the risk of PHPT deterioration postpartum and the risk of neonatal tetany. The second trimester is recommended as the optimum time for surgery after all the fetal systems have developed, and the fetus has time to allow for recovery of his own parathyroids, thus reducing the risk of neonatal tetany. Previously surgery during the third trimester has been reported to increase the risk for preterm labor [113] and other severe complications, although the occurrence of these complications could be due to the longstanding hypercalcemic status of both the mother and the fetus [63, 113]. Others do not mention any increased risk of maternal or neonatal complications [334–336].

Surgical treatment should be considered early, and a minimally invasive approach preceded by preoperative localization of the parathyroid adenoma with ultrasound and intraoperative monitoring with serial PTH measurements is best suited to mitigate the risk to the mother and fetus. It is recommended to locate and identify the parathyroid adenoma before proceeding with any surgical

Table 3.6 Characteristics of pancreatic pseudocysts in pregnancy (1980–2016)

Author	Age/gravida, para/EGA	EGA when cyst was found	Size and location	Etiology	History of cyst	Management	Delivery	Morbidity and mortality
Nies	26 years old/ gravida 2, para 0/34 weeks	PP	6 cm, tail	Lipid	Remained the same size	Conservative	Vaginal PT	Pleural effusion versus pneumonia; ICU
Glueck	Gravida 1, para 0/39 weeks	PP	N/A	Lipid	N/A	Conservative	Vaginal T	Ruptured cyst, shock, ICU
Chen	28 years old/ gravida 2, para 1/31 weeks	31 weeks	4 cm, tail	Lipid	Shrunk to 2 cm spontaneously	Conservative	N/A	None
Bar-David	28 years old/ gravida 1, para 0/17 weeks	29 weeks	N/A	Lipid	Infected pancreatic pseudocyst noted at 29 weeks, disappeared by 37 weeks	Conservative	Vaginal T	Septic shock, pneumonia with mechanical ventilation, TPN, ICU
Stowell	37 years old/ gravida 3, para 2/31 weeks	31 weeks	5 cm, head; 8 cm, tail	Alcohol	Cyst in head resolved; tail cyst remained the same size	Conservative; PP cystogastrostomy	Vaginal T	TPN for 5 weeks; FGR
Ryan	35 years old/6 weeks	Present before pregnancy	6 cm, tail	Idiopathic (alcohol?)	Grew to 7 cm; shrunk to 2 cm after stent; grew to 4 cm when stent fell out; stent replaced and cyst stable until 2 months PP	Cystogastric stent placed by ERCP at 17 weeks; transpapillary stent placed at 35 weeks; PP pancreatectomy	Vaginal T	None
Beattie	20 years old/ gravida 1, para 0/24 weeks	27 weeks	13 cm, posterior to stomach	Anatomic	1 l of fluid aspirated, then daily aspirations	Percutaneous drainage at 24 weeks; PP hepaticojejunostomy	C/S PT	Cyst collapsed around drain

Eddy	24 years old/ gravida 3, para 0/26 weeks	26 weeks	6 cm, tail	GS	Grew to 15 cm	Conservative; PP pancreatectomy	C/S T	TPN for 3 weeks; splenectomy
Swisher	N/A	N/A	6 cm	Non-GS (alcohol or idiopathic)	N/A	Percutaneous drainage	N/A	N/A
Hess	25 years old/ gravida 1, para 0/31 weeks	PP	N/A	Hyperparathyroidism	N/A	Conservative	Induced vaginal PT	Initial mental status changes, hypocalcemia after neck surgery, renal failure
G gravity, *P* parity, *EGA* estimated gestational age, *N/A* information not available, *GS* gallstone pancreatitis, *PP* postpartum; *C/S* cesarean section, *T* term, *PT* preterm, *TPN* total parenteral nutrition, *ICU* transfer to intensive care unit, *FGR* fetal growth restriction								
Qin	?/G1P0/32	33 weeks	–	Lipid	None	Conservative	Vaginal PT	None
Gyokeres	28/G1P0/21	14 weeks	8 × 7.5 cm, body	Unknown	No change in size	Endoscopic cystogastrostomy	C/S PT	None
Bansal	26/G?P?/13	13 weeks	14 × 7 cm, body	Gallstones	None	Laparoscopic cystogastrostomy	Vaginal T	None
Bernica	31/G5/19	19 weeks	20 × 13 cm, body	Unknown (lipid?)	None	Endoscopic cystogastrostomy	C/S T	None

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intervention; however, if the adenoma cannot be located with imaging, neck explorations have a 95% chance of cure [67]. In one report preoperative tumor localization in pregnancy using Tc-99 m-sestamibi scanning has been successful [73]. Advantages include avoidance of unnecessary surgical exploration, decreased complication rates, and shortened anesthesia time. The low doses and short half-life minimize fetal radiation exposure. Serial intraoperative PTH measurements are easily obtained, confirm complete removal of the adenoma, and exclude multiglandular disease [194, 205].

If the parathyroid gland is in the superior mediastinum, a cervical approach with or without sternotomy could be considered. The need to remove a parathyroid gland in the mediastinum is infrequent [332]. Although the removal of an ectopic parathyroid gland through a cervical incision may be successful in many patients, a median sternotomy is often required. This procedure has the potential for causing more morbidity and is associated with up to 12–21% incidence of chest complications [337, 338]. Advancement in video-assisted thoracoscopic surgical (VATS) techniques has decreased the need for sternotomy to successfully remove these ectopic glands [339]. Also, radioguided (questionable during pregnancy) parathyroidectomy via VATS, combined with intraoperative PTH assay, can be performed [340]. In comparison to median sternotomy, VATS offers all the benefits of surgical resection plus the potential of a marked decrease in general morbidity and hospital stay [339].

In patients undergoing surgical treatment, hypocalcemia, albeit transient, may occur after surgery in some cases. Serum calcium should be checked every 6 h, and if the patient develops hypocalcemic symptoms, intravenous calcium in the form of calcium gluconate, 10–20 mL of a 10% solution, should be given over a period of 5–10 min. Intermittent infusions in 5% dextrose or isotonic saline and infused continuously at 1 mg/kg/h. In patients with bone disease, postsurgical hypocalcemia may be profound, and aggressive treatment is needed. These patients may need vitamin D supplementation in the form of calcitriol 0.25–0.5 μg/day for a few days before the operative intervention.

The effectiveness of the surgical intervention in the prevention of fetal and neonatal complications clearly indicates that PHPT, if successfully treated, cannot be regarded as a contraindication for consecutive pregnancies. Six of nine (67%) reported cases up to 1996 were diagnosed during the third trimester, of which four underwent neck exploration after delivery. The three cases diagnosed before the third trimester underwent surgery during the second trimester.

3.7.2.4 Biliary

See Chap. 2.

3.7.3 Therapeutic Delivery

Therapeutic delivery is performed primarily to cure the AP caused by pregnancy (hormone)-induced AP of any cause, resistant to conservative and/or surgical treatment of AP, and its cause and obstetric indications are not included in the therapeutic delivery. Additional beneficial effect of therapeutic delivery is that medications that are contraindicated during pregnancy can be introduced after therapeutic delivery. The mode of delivery is determined by obstetric factors [341].

Stimulation of fetal lung maturation in the critical period for delivery is important and includes corticosteroids. In experimental animals, administration of 17 beta-estradiol accelerates fetal lung maturation and stimulates surfactant production: the hormone increases the amount of surfactant in fetal lung lavage, increases the rate of phosphatidylcholine synthesis, depletes fetal lung glycogen, and accelerates morphological maturation of the fetal lung. Both estrogens and glucocorticoids stimulate fetal lung choline-phosphate cytidylyltransferase, an important enzyme in the regulation of phosphatidylcholine synthesis. Estrogen appears to increase the catalytic activity rather than the amount of choline-phosphate cytidylyltransferase. This action of estrogen is mediated by phospholipids [342].

3.7.3.1 Hyperlipidemia/Dyslipidemia

Because pregnancy might lead to the exacerbation of HTG in patients with familial hyperlipidemia,

delivery in resistant cases is advocated because it is estimated to lower lipid levels by 15–20% within 24 h and return them to prepregnant levels by 6 weeks postpartum [144, 311, 343]. Both cholesterol and TG concentrations decreased significantly within 24 h of delivery [344], and this was reflected in all lipoproteins. However, the morbidity from AP does not always fall proportionally. Rapid improvement [344] and worsening of hyperlipidemic AP after delivery [57] have both been described, and AP can progress to maternal death [208].

While TG levels continue to decrease rapidly returning to nonpregnant levels during the puerperium, cholesterol in low-density lipoprotein remains elevated for at least 6–7 weeks postpartum [345]. Early delivery may allow more aggressive treatment of the mother, including the use of lipid-lowering agents such as statins, which are contraindicated in pregnancy (FDA category X). Delivery also lowers intra-abdominal pressure and makes it easier to resuscitate the mother and may prevent fetal distress if AP causes rapid maternal deterioration. Also, it is easier to proceed with enteral nutrition.

> Failure of ≥2 organs in SAP has a high incidence of fetal loss and therefore early therapeutic delivery is advocated.

3.7.3.2 Gallstones and Unknown Causes

In AP due to gallstones or of unknown cause, the rapid resolution has been described after intrauterine fetal death [17] and after vaginal delivery with a live birth [346]. Fortunately, gallstone AP is successfully treated with endoscopic, surgical, or combined procedures, and delivery is indicated only for obstetric indications (most commonly fetal distress).

3.7.3.3 Preeclampsia/Eclampsia

Preeclampsia is a severe form of pregnancy-induced hypertension and can lead to the occurrence of epileptic-like grand mal convulsions (eclampsia) in 0.1% of pregnancies. The cerebral vascular accident is the most common cause of death. The disease has no known cause and can only be cured by delivery.

3.7.3.4 Acute Fatty Liver of Pregnancy

A specific treatment is not available for AFLP. The primary treatment is delivery, which typically occurs on an emergency basis after maternal stabilization via the infusion of glucose and reversal of the coagulation disturbances. Because hypoglycemia is common, glucose levels should be monitored until liver function normalizes [56]. Sometimes patients present first with fetal distress when emergent CS is performed [98].

3.7.3.5 HELLP Syndrome

As other serious diseases of pregnancy, AP caused by HELLP syndrome can only be cured by therapeutic delivery [347] or delivery due to obstetric indications.

3.7.4 Obstetric Considerations

3.7.4.1 Prevention and Treatment of Preterm Labor

See Chap. 23.

3.7.4.2 Mode of Delivery

Spontaneous vaginal delivery is the preferred route of delivery in women with AP, because CS may cause penetration of the accumulated fluids resulting in contamination, intraperitoneal leakage, and sepsis [348]. Also, hypotension during CS can exacerbate AP due to impaired pancreatic blood supply and hypoxia [349]. However, when pancreatic pseudocysts are present, CS is recommended to minimize the risk of rupture during Valsalva efforts during vaginal delivery [55, 348]. Others state that the mode of delivery in patients with associated pancreatic pseudocysts should be determined on a case-by-case basis [56] because vaginal delivery was achieved in 69% of published cases [54, 330, 350]. In a series with AFLP-induced AP, CS was performed in 67% [127]. With some exceptions [56], morbidity reported in Table 3.6 resulted from AP or its underlying cause, rather than from the pancreatic pseudocyst. Indications for termination of pregnancy include [104]:

- Obvious signs of miscarriage or premature birth
- Fetal distress or intrauterine deaths
- If the fetus can survive, choose CS timely; if the fetus is dead, make an induction of labor

3.8 Prognosis

3.8.1 General Considerations

3.8.1.1 Maternal Outcome

There were significant improvements in both diagnostic and therapeutic (surgical, endoscopic, and obstetric) modalities in pregnant population, as well as improved ICU care. In the 1970s reported maternal mortality was up to 37% while in nonpregnant patients from that period under 50 years of age was 3.1–6.6% [12, 17, 343, 351–353]. Maternal mortality through previous decades varied 20–50%, and most occurred during the third trimester [11, 12, 16]. Maternal mortality during the 20 years before millennium in Japan was 7.5%, and no maternal death has been reported since 1985 [354, 355]. Recent reports claim overall maternal mortality of less than 1% [23, 27, 38, 104], with several studies without maternal deaths [11, 21, 30, 51].

The maternal outcome depends on several factors, some are the same as in general population:

- Pancreatitis severity
- Pancreatitis etiology
- Trimester
- Maternal age
- Maternal comorbidities

These prognostic factors are interrelated. Most importantly, the severity of AP during pregnancy depends on the cause of AP.

Non-gallstone AP had worse maternal and fetal outcomes than simple gallstone AP.

One of the explanations for better maternal and fetal outcomes is a higher trend of cholecystectomy in pregnant women who developed AP or symptomatic cholelithiasis/cholecystitis especially in early trimesters [23, 27, 30]. This supports the high relapse of biliary colic and its complications during pregnancy [356]. Also, in earlier studies, the recurrent AP risks were reported to be 50–72% during the same pregnancy [21, 51]. Traumatic, hyperlipidemic, and alcohol-induced AP has particularly poor outcomes [23]. Post-ERCP AP does not adversely affect pregnancy-related outcomes [27].

More than 90% of the women developed AP in the last two trimesters, and almost all SAP cases were in the third trimester [18, 27, 29]. The large uterus limits gallbladder motility and also produces pancreatic ischemic injury. Estrogen-related increases in serum TG levels produce the hyperviscosity which is supposed to lead to ischemia and acidosis in pancreatic capillaries [357, 358]. Changes in bile composition secondary to high estrogen levels in the last trimester may induce the formation of gallstones and sludge [357], which are the main causes of AP.

Aging is associated with increased severity of AP characterized by augmented and prolonged pancreatic inflammation and the presence of multiple extra-pancreatic sequelae including thrombosis [359]. Serious maternal pulmonary complications are often associated with AP. The destruction of pulmonary surfactant by degradation of lecithin accompanied with an increase of serum PLA2 results in increased capillary permeability of the lung and the elevation of surface tension. This leads to pulmonary edema which is considered an important etiopathogenic factor of acute respiratory insufficiency [360]. It is not known whether this mechanism is responsible for perinatal morbidity and mortality.

3.8.1.2 Fetal Outcome

In the past decades, high perinatal mortality rate, up to 50% [12], resulted from neonatal deaths after preterm delivery. Mortality rates improved in the

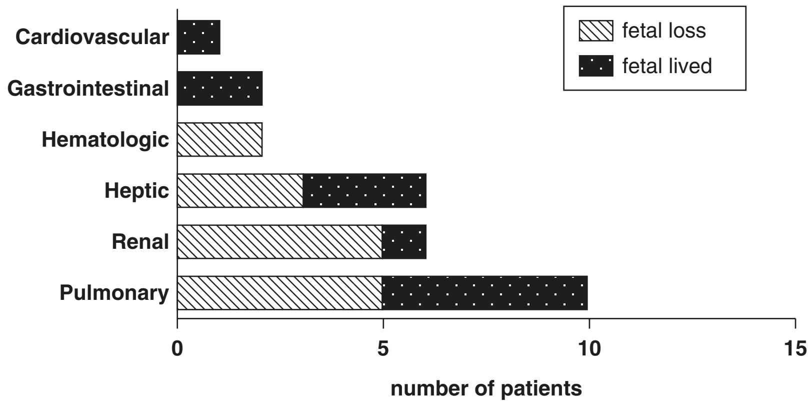

Fig. 3.27 Distribution of organ failure during acute pancreatitis in pregnancy. Reproduced with permission from [30]

last 20 years, as earlier studies reflected fetal deaths after preterm delivery which has reduced as a result of improved neonatal intensive care and better supportive treatment of AP [11]. Outcomes for the mother and fetus in 1970 were similar to 21% maternal mortality rate and 20% fetal mortality rate [343]. From the 1990s, perinatal mortality rates were improved with up to 74% of healthy term deliveries with 10.5–17% of fetal mortality rate [11, 145]. Even preterm babies delivered by CS could be saved due to improvements in perinatal care. Recent studies claim perinatal mortality rate of 0.57–4.7% [21, 23, 361] and 19% of preterm labor [21]. The fetal outcome depends on the:

- Trimester
- The severity of AP
- The cause of AP
- Organ failure dependent

It is important that most publications do not distinguish between the various causes and severity of AP. In a Turkish study, nearly half of the patients had SAP, and in contrast to the MAP group, where 57% of the deliveries occurred beyond 37 weeks, in the SAP group, 83% of deliveries occurred prematurely. This finding is consistent with the study of Geng et al. with the fetal loss of 33%, preterm delivery rate of 39% among SAP patients [30]. Also, the term delivery rate in the MAP group was significantly higher than in the SAP group, while the fetal loss was different between MAP and SAP [18]. Late abortion (70%) and preterm infants (30%) constituted the fetal loss in MAP group, while fetal death and stillbirth were the main fetal loss components (83.3%) in the SAP group [18]. In light of these findings, prematurity seems to be related to the severity of AP. Some studies did not find the statistical difference of fetal death and preterm births between biliary and HTG-induced AP [145]. On the other hand, MAP was more common (77%) variant in biliary AP [145]. Placental abruption/uteroplacental apoplexy induced by AP is very rarely reported [362, 363]. Placental abruption likely occurs in the first phase of AP, resulting from a systemic inflammatory response.

Patients who developed AP in the first trimester have the lowest percentage probability to reach term pregnancy (60%) and the highest risk of fetal loss (20%) [22, 27]. Preterm labor may occur in as many as 60% of patients who have AP in late pregnancy; therefore, gestational age is a primary determinant of perinatal outcome.

Fetal outcome is organ failure dependent. If two or more organ systems are involved, there is the highest risk for fetal loss [30]. Figure 3.27 shows the distribution of the failure of organs. The lung was the most vulnerable organ; the kidney and the liver were also easily affected. Renal and coagulation disorders denoted poor prognosis, whereas gastrointestinal and cardiovascular dysfunctions were not so common in SAP.

The mechanisms of demise include, also, placental abruption and profound metabolic disturbance, including acidosis. Altered maternal acid-base status can adversely affect fetal acid-base status. Acute fetal hypoxia activates some compensatory mechanisms for redistribution of blood that enable fetus to achieve a constancy of

oxygen consumption in the fetal cerebral circulation and in the fetal myocardium. Redistribution of blood to vital organs enables fetus to survive for a moderately long period of limited oxygen supply, but during more severe or sustained hypoxemia, these responses were no longer maintained and decompensation with fetal tissue damage and even fetal death may occur [49, 361].

AP complicated by DIC usually occurs in the third trimester and is particularly associated with poor fetal outcomes [27]. Hepatobiliary diseases can result in maternal and fetal physiological dysfunction, leading to adverse pregnancy outcomes, such as prematurity and low birth weight [364]. Thus, it is particularly important to identify hepatobiliary disease early during pregnancy and to intervene appropriately as early as possible.

3.8.2 Primary Hyperparathyroidism

Postoperative (parathyroidectomy) pregnancy outcomes showed a four- to fivefold decrease in maternal/fetal complication rates [73]; therefore surgical therapy is recommended.

3.8.2.1 Maternal Outcome

Untreated severe PHPT during pregnancy without AP has been reported to result in maternal complication rates as high as 67% [67]. Clinically significant complications related to PHPT were as high as 25% in the medically managed patients compared to 12.5% in the surgically managed patients [73]. Increased risk for mother complications apart from AP include visceral calcification particularly nephrolithiasis/nephrocalcinosis (24–36%), generalized weakness, hyperemesis, muscle cramps, bone resorption (subperiosteal resorption (especially on the radial aspect of the middle phalanges of the hand), preeclampsia/eclampsia, and lethargy/psychiatric problems (irritability, depression, and marked insomnia) [67, 77]. If the mother is treated medically to term (or if a spontaneous or elective abortion occurs), the mother should be monitored for *hypercalcemic crisis* postpartum present in the early postpartum period due to the sudden interruption of the transplacental shunting of calcium from the mother to the fetus [62, 67]. It is the most feared and life-threatening complication of PHPT during pregnancy and can be seen with serum calcium levels >14 mg/dL and is characterized by nausea, vomiting, tremors, dehydration, and mental status changes which can progress to uremia, coma, and even death [77].

Up to 1998 and from the 13 patients with AP due to PHPT, maternal mortality was 15% [89]. Mortality seems to be related to delayed resection of parathyroid tumor [89]. Hypercalcemic crisis can occur if emergent CS is performed during AP in pregnancy during pancreatic necrosectomy and drainage.

3.8.2.2 Fetal Outcome

Untreated severe PHPT during pregnancy results in fetal complication rates as high as 83% and neonatal complication rates as high as 53% (of which about 30% represent neonatal deaths) [67]. The complications include intrauterine/neonatal demise, second-trimester loss, and generalized tetany after delivery [77]. It was found that patients with calcium levels of 10.7 mg/dL were associated with pregnancy loss, but most pregnancies continued to term. Calcium levels >11.4 mg/dL were associated with higher levels of fetal loss, and 72% of fetal loss occurred at or above this level [365]. In a retrospective analysis of 109 cases reported of PHPT during pregnancy from 1930 to 1990, 70 patients were treated medically, whereas 39 patients had surgery during pregnancy [60]. Among patients, those who were treated medically, 53% of neonates had complications and 16% died. In contrast, in the group managed surgically, 12.5% of neonates had a complication and only 2.5% died. Therefore, fetal mortality rate when PHPT without AP is present can be reduced by a factor of four if an operative cure is achieved [60, 67, 366]. In addition, there are studies that did not have any maternal or fetal complications after surgery [63].

Neonatal hypocalcemia with tetany is usually a transient phenomenon related to suppression of fetal parathyroid glands resulting from maternal-fetal hypercalcemia; it may be more prolonged in the mature infants or infants with birth asphyxia. PHPT results in high concentra-

tions of fetal serum calcium that act to suppress the parathyroid glands. Fetal calcitonin concentrations are high to encourage bone mineralization. At birth, however, the neonate is suddenly deprived of this source of calcium. It is incapable of mobilizing calcium from the bone owing to the low concentrations of parathyroid hormone and high concentrations of calcitonin. *Acute neonatal hypocalcemia*, first described by Friderichsen in 1939 [367], results in neonatal tetany and convulsions, usually at 5–14 days of age. If the infant is breastfed, tetany can be delayed by 1 month or more [332, 368].

In 13 patients with PHPT with AP up to 1998, fetal mortality was 23% [89]. Mortality seems to be related to delayed resection of parathyroid tumor [89].

3.8.3 Acute Fatty Liver of Pregnancy

3.8.3.1 Maternal Outcome

Report from 1980 demonstrated a very high maternal mortality of 75% [369]. Recent reports indicate that with prompt diagnosis and treatment, maternal mortality rates have greatly decreased to approximately 17–18% [127, 370, 371].

3.8.3.2 Fetal Outcome

Report from 1980 demonstrated a very high perinatal mortality of 85% [369]. Recent reports indicate that with prompt diagnosis and treatment, perinatal mortality rates have greatly decreased to approximately 23–25% [127, 370, 371]. Fetal mortality is in a form of intrauterine fetal death attributed to placental hypoperfusion due to profound maternal hypotension. No evidence of growth restriction or phenotypic abnormalities suggests other causes [127].

3.8.4 Hypertriglyceridemia

3.8.4.1 Maternal Outcome

Interestingly, beyond the apparent significance of a TG threshold level to initiate AP (approximately 1000 mg/dL), the severity of HTG-induced AP or its complications does not seem to correlate directly with TG level [372]. This correlates with findings in general population. When the complete dyslipidemic group in general population is analyzed, the indices of SAP and complications were predominantly found in the HTG group, irrespective of the grade [373]. One of the explanations is that HTG is often associated with additional negative prognostic factors such as DM (the prevalence of DM in dyslipidemic AP in general population is around 30% [373]), obesity, alcohol consumption, etc. In one of the largest studies, HTG-induced AP had severe form in 77% of patients while biliary AP 44% and alcohol-induced AP 0% [18]. In another study isolated HTG-induced AP was the cause of 50% of pregnant SAP patients [30]. Therefore, HTG-induced AP in pregnancy is a serious complication and is associated with a significant risk of death for both the mother (21%) and the fetus (20%) [343]. However, in 15 cases of gestational hyperlipidemic AP, no maternal death was reported [33, 295]. Although severity and complication rates with HTG-induced AP have been reported as higher in comparison to AP from other etiologies, mortality rates have not been found to differ. In general population, patients with HTG-induced AP had significantly more prior episodes of AP in comparison with biliary AP and more complications such as pancreatic necrosis, abscess formation, sepsis, or renal insufficiency, without mortality in both groups [374]. A Recent study showed lower Ranson score in HTG group compared with biliary AP group. Also, the mortality was nil in HTG-induced AP group compared to 22% in biliary AP group. A possible explanation is an early diagnosis of HTG as a cause with immediate therapeutic interventions for lowering its serum values.

3.8.4.2 Fetal Outcome

Studies show the highest fetal mortality rate in HTG-induced AP. In some studies almost all fetal losses were due to HTG-induced AP in its severe form, resulting in 38.9% preterm delivery and 33% fetal loss rate [30].

HTG is often part of metabolic syndrome including DM. Maternal DM leads to a higher risk

of the fetus developing impaired glucose tolerance and obesity during adulthood. Maternal hyperinsulinemia and the transient hyperglycemia impair endocrine pancreas development in the control offspring and induce multiple metabolic alterations in early postnatal life. The relatively smaller β-cell mass/area and β-cell proliferation in these control offspring suggest cell-autonomous epigenetic mechanisms in the regulation of islet growth and development [375]. Fetal development in a diabetic environment is characterized by an increased insulin secretion, due to overstimulation and possibly resulting in exhaustion of the fetal pancreatic β-cells. The risk for DM is significantly higher when the mother rather than the father had non-insulin-dependent DM [376]. Furthermore, 35% of patients with gestational DM are offspring of diabetic mothers compared with only 5% of normoglycemic mothers, and gestational DM occurs more frequently in the offspring of diabetic mothers (35%) than in offspring of diabetic fathers (7%) [377]. The most common types of human structural birth defects associated with pregestational DM are congenital heart defects and central nervous system defects. However, DM can induce birth defects in any other fetal organ. In general, the rate of birth defects increases linearly with the degree of maternal hyperglycemia, which is the major factor that mediates teratogenicity of PGD. In addition, because many of the components of metabolic syndrome result in increased low-grade systemic inflammation [378], an increasing stimulation of the inflammation pathway conferred from the mother with metabolic aberrations to the fetus might explain the increased risk of medically indicated preterm births in women with metabolic syndrome in early pregnancy. Therefore, it is sometimes difficult to “accuse” only single event such as AP for adverse fetal outcomes.

3.8.5 Medications

The prognosis of drug-induced AP in general population is excellent. In one report of 22 cases, 19 were associated with interstitial AP, none of the patients with pancreatic necrosis, none over 33% of the pancreas involved, and none died [183]. Mortality has also been rare in other reviews, although there are reports of a few deaths directly related to drug-induced AP.

3.8.6 Alcohol Abuse

3.8.6.1 Maternal Outcome

Patients with alcohol-induced AP were more likely to have a recurrence of AP during pregnancy (75% vs. 29%) compared to cases where alcohol was not a factor [23]. Pseudocysts were almost exclusively associated with non-gallstone AP [23].

3.8.6.2 Fetal Outcome

Patients with alcohol-induced AP were more likely to have a preterm delivery (67% vs. 26%) compared to cases where alcohol was not a factor [23].

3.8.6.3 Preeclampsia/Eclampsia

All cases of maternal deaths and intrauterine fetal demise were published before 1973 [91]. One recent case with maternal death was with rapid deterioration. Unfortunately, serum/urine amylase and lipase were not taken during the course of the disease and also authors did not perform the abdominal CT scan [379].

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4 Gastrointestinal Perforation

Abstract

Gastrointestinal perforations of the upper gastrointestinal tract are extremely rare. Peptic ulcer symptoms decrease during pregnancy due to healthier maternal habits during pregnancy in addition to pregnancy-induced hormonal gastroprotection. On the contrary perforations of the lower intestinal tract are more common due to spontaneous, disease-induced, and postinterventional perforations. Aside of intestinal endometriosis-induced perforations, the most common are postinstrumental perforations for termination of pregnancy. This is seen in a form of transuterine bowel perforation and is more common in undeveloped and developing countries where illegal abortion is relatively frequent. It is a complex injury necessitating simultaneous obstetric and surgical management. Extension of bowel injury determines maternal outcome and quality of life.

4.1 Perforated Peptic Ulcer

4.1.1 Peptic Ulcer in General

I have never seen undue activity of a peptic ulcer during pregnancy, but I am very familiar with the opposite state of affairs where ulcer symptoms disappear during pregnancy.

George Grey Turner

4.1.1.1 Historical Perspective

The first known peptic ulcer was found in China in a corpse 2200 years ago [1] with increasing frequency since then. But there is this gap of 2000 years since the Greeks started Western medicine and conceived that abdominal pain could be due to an ulcer inside the stomach lining akin to ulcers they were familiar with on the rest of the body. The testing of this hypothesis could, of course, come only from necropsies from about the fifteenth century, when ulcers, first gastric, then in the eighteenth century duodenal, were recorded and became more common and, then later, less frequent in most age groups [2]. The first modern description of bleeding peptic ulcer was by Mulsow and Brown in 1936 [3].

4.1.1.2 Incidence

There are approximately 500,000 new cases and 4.5 million people suffering from these diseases each year in the United States.

Women vs. Men

The ratio between men and women who develop duodenal ulcer is 1.9:1 in the United States, whereas in Europe and Asia, this ratio is 2.2:1 [4, 5] and 3.1:1 [6], respectively. Incidence in pregnancy is extremely low due to several factors (see further text).

Decade Dependency

With time, there has been a dramatic fall in the prevalence of peptic ulcer disease (PUD) in

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_4

developed countries. The dramatic decline in reported hospitalization and mortality rates for PUD in the United States started around the 1960s in general population. There is an approximately 30–40% fall in hospitalizations for PUD complications between 1993 and 2006 with a larger reduction in duodenal ulcers (−37.2%) than gastric ulcers (−19.6%) [7, 8]. Duodenal ulcer is more common than a gastric ulcer, although the largest decreases in ulcer incidence have been seen in duodenal ulcer [9]. Despite a declining incidence overall of PUD, the incidence of PUD complicated by either bleeding or perforation has remained constant or in fact even increased. Although the data are inconsistent in different countries, data from Finland and the Netherlands suggest that the rate of ulcer complications and the need for emergent ulcer surgery may have increased slightly over the past 30 years [7].

Incidence in Pregnancy

Reports from the twentieth century have highly variable incidence. Cappell and Sidhom reported that 0.19% of pregnant patients who were hospitalized were found to have severe upper gastrointestinal complaints [10]. Only 2/20 women undergoing esophagogastroduodenoscopy (EGD) were identified as having PUD (specifically duodenal ulcers). Tests to evaluate suspected PUD (e.g., upper gastrointestinal series or EGD) that are routine in the general population have been conservatively performed on pregnant women [11]. At the Central Middlesex Hospital, London, during the 11-year period (1951–1961), the incidence of duodenal ulcer was 1/11,497 confinements; the same incidence of 1/11,497 confinements was for gastric ulcer and for simultaneous peptic ulceration and hemorrhage (with additional dyspepsia in three and gastritis in three) patients [12]. Sandweiss et al. [13] found PUD in 1/70,310 pregnancies, Johnston [14] in 1/6021 and Durst and Klieger [15] in 1/24,915. In England and Wales (1951–1960), 0.58% of all deaths associated with pregnancy were due to PUD [16], while 0.3% of all deaths from all causes in women aged 20–49 were due to PUD [17]. Duodenal ulcers in early pregnancy are extremely rare (see Sect. 4.1.1.3). In a 15-year period, there were five published cases [18, 19].

On the contrary, there is a higher incidence of maternal dyspepsia during pregnancy in comparison to general population. Dyspepsia is among the most common gastrointestinal diagnoses and is estimated to occur in 14–20% of adults [20, 21]. Dyspepsia is a very common symptom in pregnancy, particularly in the second part, when 21% of pregnant women complain of heartburn daily, 52% at least once a month, and as many as 80% in the third trimester [22, 23].

4.1.1.3 Pathophysiology

In the beginning of the twentieth century, it was claimed that the symptoms of PUD, and presumably its activity, are influenced by menstruation and by pregnancy. Thus Taussig, Sutherland, and Szenes have suggested that menstruation causes an exaggeration of the symptoms of PUD, while Mussey, Crohn, Hurst and Stewart [24], and many others have claimed that pregnancy commonly has a beneficial effect. It may well be that the remission of PUD symptoms in pregnancy is related to the general feeling of well-being, success, and fulfillment characteristic of that state, while the mental stresses, irritability, and emotional imbalance of the menopause may account for the renewed ulcer activity at that time. It is well established that pregnancy is a period of increased hormonal activity with a marked increase in the gonadotrophic, luteal, and estrogenic hormones, while the menopause is associated with a diminution in the sex hormones and particularly the estrogens.

Dyspeptic symptoms usually disappear about the end of the third month of pregnancy, but they may persist till term. The estrogen level and the greatly elevated histaminase concentration afford part of the explanation why symptoms, and especially complications, from PUD, are so rare during pregnancy. Occasionally, more severe indigestion occurs with a considerable resemblance to an ulcer. Sandweiss et al. in 1939 reported 52 pregnancies in 25 women who were known to have PUD. In all but one case, the ulcer symptoms disappeared during pregnancy [25]. Clark in 1953 investigated dyspeptic symptoms

during 313 pregnancies in 118 women diagnosed as suffering from PUD before pregnancy. There was a remission of PUD symptoms in 88% of the pregnancies. More than half of these women claimed to have been completely symptom-free during the whole pregnancy; the remainder had minor symptoms which they regarded as unconnected with the ulcer. In the remaining 12%, symptoms persisted which were indistinguishable from those of ulcer, and 1/3 of these were admitted to hospital for treatment of "indigestion," but in some of these patients, albuminuria was found and there was no proof of PUD. In no case did hemorrhage or perforation occurred during the pregnancy [26]. Therefore it appears that in almost 90% of PUD patients, symptoms are in abeyance during pregnancy.

Unfortunately, the benefits derived from pregnancy in women with PUD are apparently short-lived with almost 100% recurrence within 2 years postpartum (Fig. 4.1).

Gastric Position Changes

Hurst and Stewart in 1929 stated that pregnancy exerts a favorable influence on the symptoms of a PUD and in some cases appears to lead to actual healing apart from any specific treatment. This they attributed to the mechanical effects of support of the stomach by the rising uterus. This is supposed to relieve the strain on the lesser curvature and improve the local circulation, which promotes healing of any ulcer [24]. In several cases [3, 27], the major accidents took place at a time when the stomach could not have been lifted much higher in the later weeks of pregnancy. Therefore, the mechanical theory by Hurst and Stewart is questionable.

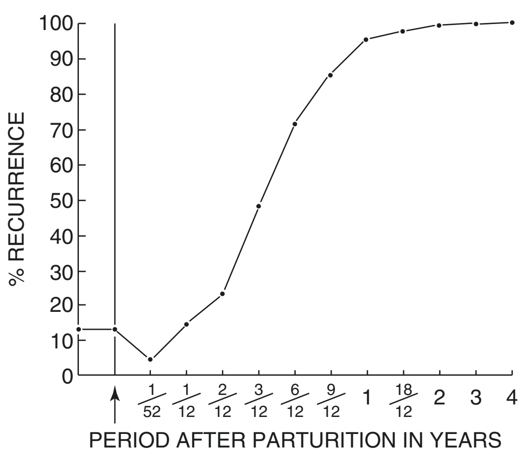

Fig. 4.1 Recurrence of peptic ulcer symptoms after parturition. Reproduced with permission from [26]

Hypochlorhydria

Balint in 1927 [28] first suggested a general tendency toward increased alkalinity in tissue fluids during pregnancy, and other observers have confirmed that with increased alkalinity, there is found a hypo- or even achlorhydria, especially in the first 6 months of pregnancy; thereafter, the acid values rise toward normal and might even reach supernormal figures in the puerperium in certain cases [29–31]. The earliest observations on gastric acidity in pregnancy were made in 1925 by Nakai, who showed that there was a striking diminution in both the free and the total acid content of gastric juice in response to a test meal [29]. This was confirmed by Artz [31], who drew attention to the fact that the lowest secretion of free acid coincides with the period of pregnancy when nausea and vomiting are common. Murray et al. noted with the maximal histamine test that maximal secretion was decreased in the first 30 weeks of pregnancy [32]. This decreased secretion could be due to several factors. Plasma diamine oxidase (histaminase) levels are markedly increased in pregnancy [33], and there is evidence from the 1960s that this substance is related to gastric secretion and may inhibit it [34]. Another important observation is that regurgitation of duodenal contents especially bile is present in only 3% of pregnant patients despite common nausea and vomiting during (early) pregnancy [30, 35]. Authors share the opinion that duodenal regurgitation is not the cause of hypochlorhydria.

Hormones

Crohn (1927) and others noted that peptic ulcers tend to break down in the puerperium. Winkelstein (1940) thought that the agent responsible for the breakdown might possibly be prolactin, the lactogenic hormone of the anterior pituitary. During gestation, the formation of prolactin is inhibited

by the high blood levels of ovarian and placental hormones. He made experimental studies on animals with chemically produced peptic ulcers by treating them with the ovarian hormone theelin. The response was good and the ulcers healed within 10 days.

Administration of progesterone protects the gastroduodenal mucosa against ulcerogenic treatment with cysteamine or indomethacin. This last finding is in agreement with the data showing that an increase of endogenous progesterone levels by early pregnancy or the administration of exogenous progesterone decreases the vulnerability of gastroduodenal mucosa to cysteamine [36]. Interestingly, progesterone acts as a protective factor also in male rats.

The maximal levels of chorionic gonadotropins also correspond to the period of decreased gastric secretion. The increased level of estrogen may be a factor, and stilbestrol does have a beneficial effect on duodenal ulcers [37]. The equal sex incidence of peptic ulceration in children, the decreased incidence in women during the childbearing years, and the marked increase in incidence at the time of menopause [38] all suggest that the female sex hormones have some relationship to PUD and that the alterations in the hormones during pregnancy may give rise to an increased resistance to PUD. Duodenal ulceration and its complications in the presence of high blood levels of both estrogens and progestogens must be due to factors other than changes in acid output. Protection against gastric ulceration during pregnancy in rats in the presence of raised acid output has been observed [39].

Plasma pepsinogen rises in the last trimester of pregnancy, reaching a maximum on the first postpartum day [40]. There is a decreased secretory response to histamine acid phosphate during pregnancy, mainly during the first 30 weeks [32]. Two possible explanations for diminished hydrochloric acid secretion have been offered. The first is the antisecretory effect of plasma histaminase, which increases in pregnancy, sometimes as much as 1000-fold [41]. Plasma histaminase begins to rise about 7 weeks after the last normal menstrual period and that the peak is reached in the 26th–28th weeks of gestation [33]. Preparations of histaminase administered to dogs with Heidenhain pouches were shown to diminish histamine-stimulated secretion [41].

Way, in 1945, attempted to explain the rarity of PUD and complications in pregnancy by correlating the hypochlorhydria found in these patients with the increased secretion of the anterior pituitary-like hormones in the urine. He concluded that the greater the secretion of these latter, the more marked the hypochlorhydria. This endocrine explanation appears to be the most likely reason for the rarity of PUD activity during pregnancy [35, 42]. Hormonal changes characterized by significant increases in levels of 17-hydroxysteroids and 17-ketosteroids have also been implicated as a possible factor in PUD in late pregnancy [42]. These and other observations suggest that estrogens may protect against peptic ulceration. This concept is supported back in 1960 by the beneficial effect, demonstrated in when stilbestrol was used in the treatment of men with duodenal ulcer [37].

It has also been suggested that female gestational hormones (progesterone in particular) decrease the rate of ulcer formation by increasing gastric mucus synthesis. An increase in plasma histamine in pregnancy (caused by placental histaminase synthesis) increases metabolism of maternal histamine, thereby reducing gastric acid secretion during pregnancy [33].

Fertility Rate and Peptic Ulcer

One of the causes of the rarity of PUD in pregnancy is that patients with duodenal ulcer, regardless of sex, have a 25% lower fertility rate compared to the general population (at least in the era before methods of assisted reproduction) [43]. PUD reduces the reproductive ability in the sense that the number of children born to affected probands as well as affected parents is smaller than to unaffected individuals. The finding was supported by the observation that the number of children of patients with PUD was not influenced (i.e., further reduced) by a positive family history of PUD. By contrast, detailed analysis revealed that childlessness was more frequent in affected

probands with a positive family history of PUD than in affected probands with a negative family history: 26% compared to 16%, respectively. A positive family history has thus been shown to participate in the higher rate of childless marriages for subjects suffering from PUD. At the same time, it has no bearing on the number of children who are born. The number is, however, reduced compared to the average for the general population, as a result of the probands' disease.

There is a possibility that PUD and reduced fertility rate are not directly bonded. Observation from 1939 showed that 46.7% of women with PUD showed pituitary, thyroid, or gonadal abnormalities [25]. During the first half of the twentieth century, it was stated that the female patient with PUD should be surveyed from the standpoint of endocrine abnormality. Therefore, underlying endocrinopathies could be (partly) responsible for the reduced fertility rate.

4.1.1.4 Risk Factors

All known risk factors for PUD in general population are also risk factors in the pregnant population.

Helicobacter pylori Infection

See Sect. 4.1.1.9.

Medications

NSAID use is a common cause of PUD. These drugs disrupt the mucosal permeability barrier, rendering the mucosa vulnerable to injury. Around 30% of adults taking NSAIDs have adverse GI effects. Factors associated with an increased risk of duodenal ulcers in the setting of NSAID use include the history of previous PUD, advanced age, female sex, high doses or combinations of NSAIDs, long-term NSAID use, concomitant use of anticoagulants, and severe comorbid illnesses. Although the idea was initially controversial, most evidence now supports the assertion that *H. pylori* and NSAIDs are synergistic with respect to the development of PUD. *H. pylori* eradication in NSAID-naive users before the initiation of NSAIDs is associated with a decrease in PUD [44].

Corticosteroids alone do not increase the risk for PUD; however, they can potentiate ulcer risk in patients who use NSAIDs concurrently.

Lifestyle Factors

Evidence that *tobacco* use is a risk factor for duodenal ulcers is not conclusive. Support for a pathogenic role of smoking comes from the finding that smoking may accelerate gastric emptying and decrease pancreatic bicarbonate production. Studies have produced contradictory findings. Smoking is harmful to the gastroduodenal mucosa, and *H. pylori* infiltration is denser in the gastric antrum of smokers [45].

Ethanol is known to cause gastric mucosal irritation and nonspecific gastritis. Evidence that consumption of alcohol is a risk factor for duodenal ulcer is inconclusive.

Little evidence suggests that *caffeine* intake is associated with an increased risk of duodenal ulcers.

Severe Physiological Stress

Stressful conditions that may cause PUD include burns, CNS trauma, surgery, and severe medical illness. Serious systemic illness, sepsis, hypotension, respiratory failure, and multiple traumatic injuries increase the risk for secondary (stress) ulceration. Cushing ulcers are associated with a brain tumor or injury and typically are single, deep ulcers that are prone to perforation. They are associated with high gastric acid output and are located in the duodenum or stomach. Extensive burns are associated with Curling ulcers. Severe illness and a decreased gastric pH are related to an increased risk of gastric ulceration and hemorrhage.

Hypersecretory States

The following uncommon hypersecretory states may cause PUD:

- Gastrinoma (Zollinger-Ellison syndrome) or multiple endocrine neoplasia type I
- Antral G-cell hyperplasia
- Systemic mastocytosis
- Basophilic leukemias

- Cystic fibrosis
- Short bowel syndrome
- Hyperparathyroidism

Fasting (General Population)

The frequency of PUD in general population is increased during Ramadan, as well as PUD complications are more frequent during Ramadan, compared to periods before and after Ramadan [46]. There is one case of perforated duodenal ulcer during Ramadan in pregnancy [47].

Additional Risk Factors

Other risk factors may be associated with PUD and are listed in Table 4.1.

4.1.1.5 Clinical Presentation

PUD is rare and difficult to diagnose during pregnancy. The beneficial influence of pregnancy upon PUD symptoms has been adequately confirmed back in 1903 by Chabannes [48]. Obstetric patients, as a rule, are not questioned closely with respect to past gastrointestinal symptoms. Epigastric distress, heartburn, nausea, and vomiting are frequent complaints during normal pregnancy and, therefore, often overlooked. These symptoms are also associated with hyperemesis gravidarum and hiatal hernia, both more prevalent than PUD in pregnancy. On the contrary to PUD itself, dyspepsia is among the most common gastrointestinal diagnoses and is estimated to occur in 14–20% of adults [20, 21]. Dyspepsia is a very common symptom in pregnancy, particularly in the second part, when 21% of pregnant women complain of heartburn daily, 52% at least once a month, and as many as 80% in the third trimester [22, 23].

Cardinal symptoms of PUD are an upper abdominal pain, nausea, and vomiting. The pain is often epigastric and worse at night. In the presence of a gravid uterus (and especially when labor ensues), it can be quite difficult for patients to localize pain. Unlike gastroesophageal reflux disease, the pain is not exacerbated by recumbency or associated with regurgitation. Although nausea and vomiting occur in 50–80% of normal pregnancies, it is uncommon for these symptoms to persist beyond 20-week gestation. Nausea and vomiting of pregnancy are classically most intense in the morning, while PUD symptoms are worse nocturnally and postprandially during the day. PUD symptoms also get worse with increasing gestation and are therefore usually most severe in the third trimester. Occasionally, PUD may present with hematemesis. Uncomplicated PUD produces minimal physical signs. The symptoms of PUD are improved during pregnancy in many women. Relief occurs early in pregnancy, but unfortunately, the symptoms frequently recur following delivery (Fig. 4.1) [27].

Table 4.1 Less common causes of peptic ulcer disease in general population

Hepatic cirrhosis
Chronic obstructive pulmonary disease
Allergic gastritis and eosinophilic gastritis
Cytomegalovirus infection
Graft versus host disease
Uremic gastropathy
Henoch-Schönlein gastritis
Corrosive gastropathy
Celiac disease
Bile gastropathy
Autoimmune disease
Crohn's disease
Other granulomatous gastritides (e.g., sarcoidosis, histiocytosis X, tuberculosis)
Phlegmonous gastritis and emphysematous gastritis
Other infections (Epstein-Barr virus, HIV, *Helicobacter heilmannii*, herpes simplex, influenza, syphilis, *Candida albicans*, histoplasmosis, mucormycosis, and anisakiasis)
Chemotherapeutic agents, such as 5-fluorouracil (5-FU), methotrexate (MTX), and cyclophosphamide
Local radiation resulting in mucosal damage
Cocaine, which causes localized vasoconstriction

4.1.1.6 Diagnosis

Diagnostic modalities are the same for the pregnant and general population. The most common diagnostic tool during the nonemergent presentation is EGD because it can obtain samples for histopathological examination as well as *H. pylori* presence. The procedure is safe in pregnancy if no sedative medications are used which can lead to fetal hypoxia [49]. *American Society for Gastrointestinal Endoscopy* (ASGE) guidelines state two indications for EGD:

- Significant or continued GI bleeding
- Severe or refractory nausea and vomiting or abdominal pain

Therefore, if only uncomplicated PUD is suspected, there is no need for endoscopy during pregnancy, or it should be postponed until the second trimester [50].

4.1.1.7 Treatment

Pharmacological treatment is the same in pregnant and general population (see Sect. 4.1.2.5). All classes of medications are safe for the fetus, and no increase in the incidence of fetal anomalies was found [51]. No severe side effects were observed in any of the mothers or their newborns. No malfunctions or malformations were observed in the newborns. Follow-up of the children between 2 and 12 years showed normal development in all children [52]. The higher rate of congenital anomalies was not found in the offspring of mothers with PUD [51]. One study showed the possible risk of isolated rectal/anal atresia/stenosis [53].

4.1.1.8 Prognosis

Perforated gastroduodenal ulcers in pregnancy, as in nonpregnant condition, should be divided into benign peptic ulcers, malignant ulcers/perforated carcinomas, and specific forms such as Zollinger-Ellison syndrome. The division is necessary because therapeutic principles and prognosis between these groups are different. Nationwide, population-based study revealed that maternal PUD was independently associated with a 1.18-, 1.20-, and 1.25-fold increased risk of having babies with low birth weight, preterm delivery, and small for gestational age, respectively, after adjusting for family income and maternal, paternal, and infant characteristics.

With the comparison of the PUD women without treatment with the unaffected mothers, gestational PUD was found to have an adverse impact on pregnancy outcomes. Authors were unable to identify improved effects of PUD medications on the risks of adverse neonate outcomes [54]. It remains unclear what factors elevate the risk of adverse birth outcomes among patients with PUD. Glucose, transmitted from the mother to fetus, is the main energy substrate for intrauterine growth [55]. Whereas glucose is produced by maternal metabolism, dietary restriction or maternal hypoglycemia decreases the availability of metabolic fuel and consequently slows fetal growth [56, 57]. In response to symptoms of anorexia, abdominal distention, epigastric pain, and postprandial vomiting, mothers with PUD during pregnancy may restrict their dietary intake to avoid the discomfort. The risk of constrained fetal growth and adverse birth outcomes might be elevated accordingly. Stress might also contribute to the link between gestational PUD and adverse pregnancy outcomes. Stress is strongly associated with PUD because threats to homeostasis prompt an adaptive or allostatic response [58]. Maternal vasoconstriction, resulting from the release of catecholamines in exposure to stress, might also obstruct the transmission of oxygen and vital nutrients to the fetus [59]. Fetal central nervous system and particularly glucocorticoid brain receptor development might subsequently be affected [60]. Previous literature indeed demonstrated a significant relationship between maternal prenatal stress and infants with low birth weights and decreased gestational age at birth [60]. Thus, women with PUD might be those who perceive or experience more stressful circumstances. The further exposure of their fetuses to stress and elevated levels of adrenal hormones might consequently elevate the risk of negative birth outcomes.

Furthermore, there is an increased risk of adverse pregnancy outcomes among mothers with PUD who took no medication for it during pregnancy [54]. Meanwhile, no significant difference in outcomes was observed for those who did take medication during pregnancy. The trend toward slightly increased though the insignificant risk of low birth weight and preterm birth might reflect more severe PUD symptoms among women who were prescribed PUD medication.

4.1.1.9 Specific Conditions

Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome (ZES), described in 1955, is an ulcerative disease of the upper gastro-

intestinal tract that includes high levels of gastrin and gastric acid. There is little information on the management of pregnancy in patients with pancreatic endocrine tumors such as ZES. This has occurred because the syndromes are uncommon (i.e., ten cases/million population/year); until last decades, these patients frequently died soon after the diagnosis, which was often established only late in the disease course, and the hormonal syndrome often caused severe metabolic or nutritional deficiencies that may have interfered with pregnancy. However, at present, because of earlier diagnosis and the increased ability to medically control the hormonal symptoms, especially in patients with ZES with potent gastric acid antisecretory drugs, these patients are living longer, and women with the disorder more frequently become pregnant. The tendency of the tumor to grow slowly enables the physician to focus on symptomatic treatment. Gastrin levels do not change significantly during pregnancy [61] and thus are useful for the diagnosis and follow-up of this syndrome. There is a controversy whether pregnancy offers protection against ZES. Some have reported the absence of symptoms of ZES during pregnancy [62, 63], while others reported cases of exacerbation during pregnancy that required i.v. omeprazole treatment or even operation [64, 65].

The management of pregnant patients with an asymptomatic pancreatic endocrine tumor syndrome such as ZES presents a number of unique problems. ZES is the most common symptomatic malignant pancreatic endocrine tumor. Similar to the other pancreatic endocrine tumors, these patients have two different treatment problems. First, symptoms caused by the ectopic hormonal release must be controlled, and, second, treatment must be directed against the tumor, which in all the syndromes, except insulinoma, is malignant in 30–90% of cases and 34% of patients have liver metastases; however, in most patients the tumor grows relatively slowly [66]. Because of the slow rate of progression of most gastrinomas, the primary problem during pregnancy in patients with ZES is controlling the severe gastric acid secretion. This problem is complicated by the large volume of gastric acid secretion, necessitating high-dose daily gastric acid antisecretory drug treatment and the unknown high-dose safety profiles of any of the gastric antisecretory drugs during pregnancy. If the ZES is diagnosed before pregnancy, curative resection with parietal cell vagotomy may obviate the need for gastric antisecretory drugs. If metastases are present or the diagnosis of ZES is made after conception, ranitidine in the lowest possible dose should be used to control acid secretion. If acid secretion is uncontrolled, the dose may be increased or omeprazole may be used [67].

Antacids are generally ineffective in the management of ZES and thus are not a realistic option.

The histamine H_2 receptor antagonists and H^+-K^+ adenosine triphosphatase inhibitors can control gastric hypersecretion in all patients with ZES (see Sect. 4.1.2.5); however, high doses of these drugs are frequently required. The high doses used in ZES cimetidine can cause antiandrogen side effects [68]. Ranitidine, however, has not been shown to possess these antiandrogenic effects even at high doses [69]. There are case reports describing the safe use of cimetidine and ranitidine in pregnant patients with ZES [70]. The detailed strategy of treating patients with ZES prior to and during pregnancy could be found in the article by Stewart et al. [67].

Helicobacter pylori

H. pylori infection and NSAID use account for most cases of PUD. The rate of *H. pylori* infection for duodenal ulcers in the United States is less than 75% for patients who do not use NSAIDs. Excluding patients who used NSAIDs, 61% of duodenal ulcers and 63% of gastric ulcers were positive for *H. pylori*. These rates were lower in whites than in nonwhites. Prevalence of *H. pylori* infection in complicated ulcers (i.e., bleeding, perforation) is significantly lower than that found in uncomplicated PUD.

H. pylori infects the human stomach, causing gastritis, peptic ulcer, and gastric cancer. *H. pylori* infection has also been related to extragastric disorders. During pregnancy, preferential induction of Th_2-type cytokines downregulates

Th_1-type responses, allowing fetal survival. The results suggest that *H. pylori* infection can induce activation of resident uterine immune cells and/or recruitment of cells at the endometrial level. It can be hypothesized that the local Th_1-type response induced by *H. pylori* infection could alter the systemic Th_1-/Th_2-type cytokine balance at sites under particular physiopathological conditions of active tissue and/or vascular formation, such as pregnancy. This is the first evidence in an animal model of the possible influence of *H. pylori* infection on pregnancy. Transmission of *H. pylori* infection from the mother to infant was not detected by culture in an animal study, suggesting that decreased baby weight may be due to decreased milk supply or altered nutrition from the mother [71]. Physiological and epidemiological evidence suggests that *H. pylori* may interfere with iron metabolism, lowering it [72]. The reduction of hemoglobin levels during pregnancy in the presence of *H. pylori* infection seemed to be slightly higher among women with iron therapy during pregnancy compared with women without [73]. Even though the difference between both groups was not statistically significant, this pattern would be consistent with the hypothesis of a possible increase in bacterial density by iron therapy, which might in turn reduce the benefit from iron therapy, because microbiologic and ferrokinetic studies suggested that outer membrane receptors of *H. pylori* in vitro are able to capture iron from human lactoferrin and use it for growth [74]. However, this hypothesis must be confirmed. Women who were infected with *H. pylori* were generally shorter than women who were not infected. Moreover, women who gave birth to babies with intrauterine growth retardation were also shorter than women who gave birth to normal-sized babies. Many studies have shown that close contact and overcrowding among family members promote the transmission of *H. pylori* infection [75]. Therefore, the possibility exists that an infected mother may more often transmit *H. pylori* to her infant and thereby continues a vicious cycle of growth restriction.

The possible mechanisms by which *H. pylori* may affect fetal growth are speculative. However, it is conceivable that *H. pylori* may be linked with an increase in symptoms including dyspepsia, nausea, or vomiting [76], because of underlying undiagnosed PUD, which in turn may affect maternal appetite and therefore restrict the growth of the fetus, although this was not determined. Another possible mechanism linking intrauterine growth retardation with *H. pylori* infection may be the effect of chronic *H. pylori* infection upon the vascular system. Acute atherosclerotic changes have been noted in placental and uterine spiral arteries in cases with intrauterine growth retardation [77].

The *H. pylori* infection may increase platelet aggregation and fibrinogen and has an effect on lipid peroxidase [78]. Therefore, chronic *H. pylori* infection might induce vascular disease, which in turn may affect the placenta and thereby cause intrauterine growth retardation. Therefore, a direct link between PUD and abnormal pregnancy and/or fetal consequences could not be proved because acute/chronic *H. pylori* infection and other potential confounders could have the same or even more influence on negative pregnancy outcomes. It has been shown in mice that *H. pylori-infected* mice show a decrease in implantation rates and their offspring are of low birth weight [79]. Infection with *H. pylori* cytotoxin-associated gene A (CagA)-positive strains has been shown to cause a severe inflammatory response and significant neutrophil infiltration in the gastric mucosa [80]. There is a statistically significant relationship between CagA-positive strains of *H. pylori* and early pregnancy loss (EPL) which might be explicable on the basis of general inflammatory reaction to infection.

Concentrations of IL-1β, IL-8, and TNF-α were all significantly higher in *H. pylori*-positive gastric mucosa [81]. These cytokines may cause systemic inflammation that could affect the integrity of the fetoplacental unit and threaten the welfare of the fetus (see Chap. 23).

Gastric Outlet Obstruction

Several cases have been described [82, 83]. Ideally, the operation during pregnancy should be avoided due to surgical stress and possible

postoperative nutritional deficiencies to the mother and fetus. Gastric outlet obstruction should be treated with endoscopic balloon dilatation with additional procedures such as endoscopic needle–knife radial incisions. Duration of the therapeutic effect depends on the underlying cause of the gastric outlet obstruction, but most studies report therapeutic effect in months which is enough to postpone the definitive treatment by operation after delivery [84]. If malignancy is confirmed, surgery is indicated by oncologic principles in pregnancy (see Sect. 4.2.1).

Fig. 4.2 Robert Daniel Mussey (1884–1958) is a physician in a family of six generations of physicians (cropped picture) [87]. He guided the development of an obstetrics/gynecology department at the Mayo Clinic and was Professor of Obstetrics and Gynecology there until he retired in 1950. Reproduced from Flikr, Family, Musseys and The Stockers, with permission

4.1.2 Perforated Peptic Ulcer in Pregnancy

> *I cannot remember a perforated gastric or duodenal ulcer during pregnancy.*
>
> Sir Gordon-Taylor

> *Every doctor, faced with a perforated duodenal ulcer of the stomach or intestine, must consider opening the abdomen, sewing up the hole, and averting a possible or actual inflammation by the careful cleansing of the abdominal cavity.*
>
> Johann von Mikulicz-Radecki, 1884

4.1.2.1 Historical Perspective

For thousands of years, healthy people have had acute abdominal pain, nausea, vomiting, and diarrhea followed by death in a few hours or days. Often these symptoms were contributed to poisoning, and people have been sent to prison for this. King Charles I's daughter, Henriette Anne, died suddenly in 1670 (at age 26) after a day of abdominal pain and tenderness. Since poisoning was suspected, an autopsy revealed peritonitis and a small hole in the anterior wall of the stomach. However, the doctors had never heard of a perforated peptic ulcer (PPU) and attributed the hole in the stomach to the knife of the dissector [85]. Necropsies were first allowed since 1500 and became more common between 1600 and 1800 [85]. As a consequence, more often perforation of the stomach was observed. Johann Mikulicz-Radecki (1850–1905), often referred to as the first surgeon who closed a PPU by simple closure in 1884, said: *Every doctor, faced with a perforated duodenal ulcer of the stomach or intestine, must consider opening the abdomen, sewing up the hole, and averting a possible or actual inflammation by careful cleansing of the abdominal cavity*. Robert Daniel Mussey (Fig. 4.2) was one of the first, in 1927, who reported two cases of peptic ulceration in 370 operations during pregnancy at the Mayo Clinic in a period of 10 years [86]. It is not known whether these two operations were made in elective or emergent settings.

4.1.2.2 General Population

Remarkable changes have occurred in the sex and age incidence of PUD in Northwest Europe. The fluctuations in the period 1790–1940 suggested three observable syndromes: perforations of acute gastric ulcers in young women, perforations of duodenal ulcers in young and middle-aged men, and perforations of gastric ulcers in older men [88]. Perforations began to be noted with increasing frequency at the beginning of the nineteenth century. Half of all perforations were then in young women in their 20s, and these reached a peak in the latter half of the century. They seemed to be *acute gastric ulcers*, which

caused death from perforations near the cardia or from hemorrhage [88]. By the end of the century, this condition had begun to disappear. But even in 1905, the Registrar General was able to write: *Gastric ulcer does not appear frequently as a cause of death until the attainment of the reproductive period*, *when the female rate greatly exceeds the male*, *while at later ages the male rate is in excess* [89]. The incidence of PPU during the 1940s in the two sexes was much greater in men, varying from 25:1 [90]. In the 1950s, however, there were signs that the volume of PUD had at last reached a peak and was beginning to fall. The lifetime prevalence of PPU has been estimated at 5% [91].

Trends for duodenal ulcer are similar but follow about 5 years behind. In the mid-1950s, death rates reached a plateau and then began to fall [92]. Since the war, mortality from gastric and duodenal ulcers has declined in young men and women, although up to 1962, it was still rising at ages over 65 (Fig. 4.3). One possible explanation is that the fluctuations in PUD rates represent a *cohort phenomenon* and that each generation has carried its own particular risk of bearing ulcers throughout adult life. Because of the success of medical therapy in the management of PUD, surgery has a very limited role, and elective peptic ulcer surgery has been virtually abandoned. The number of elective operations for PUD dropped more than 70% in the 1980s; 80% of these procedures were emergent operations [93]. Currently, mortality and morbidity following PPU are substantial, and mortality rates as high as 25–30% have been reported [94]. The mortality incidence doubles for every 6-h period from the time of perforation to the time of surgery; after 24 h the mortality rate is maintained at the high rate of over 60%. Sepsis is frequent and a leading cause of death [95].

4.1.2.3 Pregnancy

Historical Perspective

In pregnant population, Chabannes [48] in 1903 first drew attention to this subject, followed by Szenes [97]. This point is further buttressed by

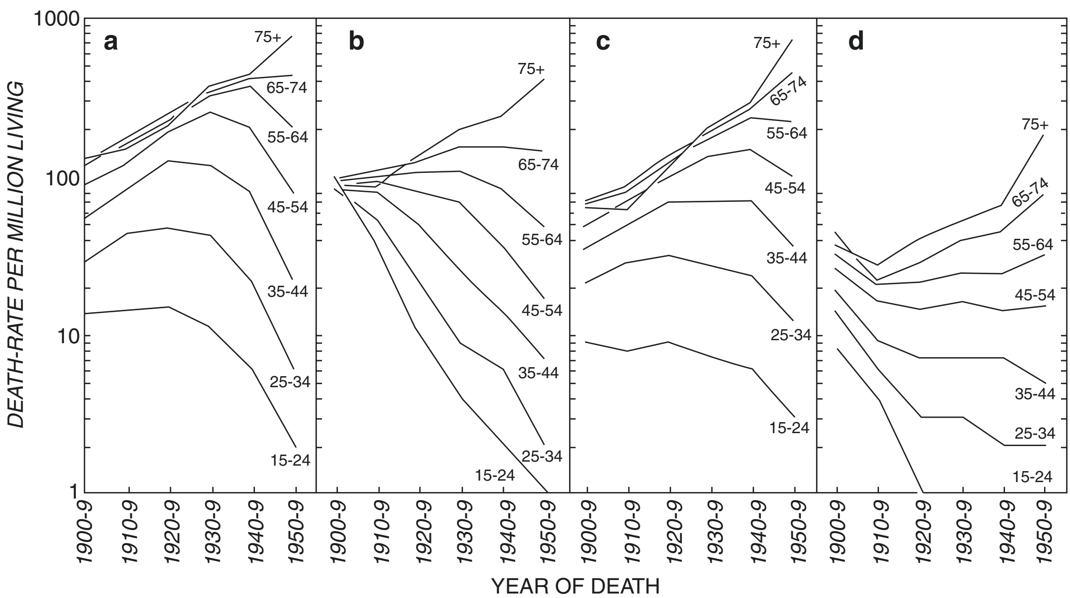

Fig. 4.3 Deaths from peptic ulcer by age and sex and year of death. (**a**) Gastric ulcer: males. (**b**) Gastric ulcer: females. (**c**) Duodenal ulcer: males. (**d**) Duodenal ulcer: females; mean rates for 10-year periods were calculated from the Annual Reviews of the Registrar General. Populations include non-civilians. Correction factors for the pre-1940 data to allow for the change in death certification (males 1.034, females 1.042) have not been used. Log graphs. Reproduced with permission from [96]

the seminal work of Hooker in 1933, in which only one case of duodenal ulcer was recorded following 1564 puerperal deaths from 348,310 pregnancies [98]. Sandweiss et al. have subsequently reviewed the topic and found nine PPUs [13]. Howkins in 1950 quoted Grey Turner's statement that "he has never seen undue activity of a peptic ulcer during pregnancy, but is very familiar with the opposite state of affairs where ulcer symptoms disappear during pregnancy" and also Sir Gordon-Taylor's statement that "he cannot remember a perforated gastric or duodenal ulcer during pregnancy [99] and it must be extremely rare to meet with this complication." Scott in 1945, discussing the differential diagnosis of acute abdominal conditions in pregnancy, does not even mention PPU [100].

Incidence

In Detroit, in the period 1928–1937, the incidence of perforated duodenal ulcer was 1/70,310 pregnancies, and of perforated gastric ulcer was 1/348,310 pregnancies over a period of 3 years in New York. Both patients died [13]. The low incidence of PUD in pregnancy has been demonstrated in a number of series from 1939 to 1955; the incidence of PUD was 11/233,650 deliveries [15, 101, 102], and among 1564 maternal deaths in 348,310 pregnancies, only one death was due to PUD [103]. In early reports, PPU was more frequent than bleeding during pregnancy [13]. Up to 1962, there were 13 cases of complicated PPUs (nine duodenal and four gastric) during pregnancy and the first week after delivery [104]. The mortality was 69% [27, 42, 105, 106]. Up to 1966 there were only 24 cases [13, 14, 17, 27, 42, 90, 105–111]. Up to 1971, 31 perforations (and 32 cases of hemorrhage) proved from PUD during pregnancy [112]. In the last 20 years, there are several more cases published (Tables 4.2 and 4.3).

Risk Factors

Risk factors for PPU are the same as for the PUD itself. Fasting (Ramadan) can be a risk factor [47]. Even a case of perforated gastric ulcer was described after adjustable gastric banding. The case does not define localization, macroscopic appearance, and whether the ulcer was peptic or related to silicone ring and local ischemia (*marginal ulcer*) [113].

Ulcer Type

Most cases during pregnancy are located in the first part of the duodenum on the anterior surface which is a common presentation in young nonpregnant population (Table 4.2).

Clinical Presentation

Clinical presentation is similar to nonpregnant population: acute and severe abdominal pain and sometimes with vomiting with the development of pyrexia. Sandweiss et al. in 1943 stated that these signs during the second and third trimester along with a history of the preexisting ulcer should be considered as "warning signals" of ulcer reactivation. Unfortunately, patients admitted to the obstetric or gynecologic services are not as a rule questioned closely with respect to past gastrointestinal symptoms even if distress exists. The history of previous PUD attacks, although difficult to obtain at times, is the most important if not single factor in arriving at a diagnosis of PUD [13].

It is difficult to notice abdominal distention in advanced pregnancy. Vital signs without the evidence of bleeding should raise a suspicion of peritonitis and septic state—raised pulse and number of respirations per minute and in the late-phase hypotension [90].

The obstetric examination is commonly normal initially, and this should also raise a suspicion of the nonobstetric cause of acute abdominal pain. Later in the course of undiagnosed peritonitis, spontaneous abortion or (preterm) labor can ensue.

Puerperium

The number of published cases can be misleading because in many cases the pain started a day or two before the labor. In many instances, the diagnosis was established during the operation after vaginal delivery. One of the first classic descriptions of puerperal duodenal PPU was by Anderson in 1942 [90]. The relative rarity of perforated duodenal ulcer in pregnancy and puerperium often causes a delay in both diagnosis and

Table 4.2 Published cases of perforated peptic ulcers during pregnancy (without puerperium)

Study	Age	Pregnancy (weeks)	Ulcer type	Duration (h)	Operation	Mother/birth	Child
Sandweiss, 1939 [25]	42	6 months	Duodenum, anterior	>24	No	Died	After 24 h, stillborn
James, 1948 [27]	24	36	Duodenum, anterior	10	Sutures	Live/vaginal	After 4 days, live
Johnston, 1953 [14]	39	Term	Duodenum, posterior	24	No	Died/emergent CS	Live
Burkitt, 1961 [106]	38	31	Duodenum	10	Partial gastrectomy	Live/vaginal	<24 h, one twin alive
Horwich, 1958 [42]	30	31	Duodenum, anterior	60	Sutures		Before operation, dead
Lindell, 1962 [107]	26	9 months	Pylorus, greater curvature, 1 cm			Live/vaginal	<24 h, live
Baird, 1966 [12]	42	15	Duodenum, anterior	<12	Sutures	Live/vaginal	37th week, live (jejunal atresia)
Winchester, 1966 [111]	21	34	Duodenum, anterior	12	Omental patch	Live/vaginal	37th week, live
Tew, 1976 [114]			Duodenum			Live	Live
Paul, 1976 [115]						Live	Live
Goh, 1995 [116]	38	35	Duodenum	24	Omental patch	Live/vaginal	Live
Hsu, 2011 [117]	23	20		96		Live/vaginal	Live
Segal, 1959 [118]	29	6	Pylorus, anterior	18	Sutures	Live, lost for follow-up after 24 weeks of pregnancy	
Essilfie, 2011 [119]	27	38	Duodenum, anterior		Omental patch	Live/vaginal	38th week, live
Gali, 2011 [47]	16	28	Duodenum, anterior		Omental patch	Live/vaginal	After 3 days, died
Ito, 2011 [120]	39				No	Live	
Ranganna, 2013 [121]	22	33	Duodenum, anterior	60	Omental patch	Died/CS	Died (twins)
Goel, 2014 [122]	25	32	Duodenum, anterior	5	Omental patch	Live/vaginal	After few hours preterm labor, dead
Amdeslasie, 2015 [123]	20	28	Duodenum, anterior	24	Omental patch	Live/vaginal	Dead (IUFD)

IUFD intrauterine fetal death, *CS* Cesarean section

surgical intervention [124]; this is made worse considering that the usual signs of perforation may be diminished or subtle in the puerperium [105, 125].

The symptoms may commonly be attributed to obstetric-related causes, and therefore, a high index of suspicion is necessary. The obstetric examination is commonly normal [90], and this should also raise a suspicion of the nonobstetric cause of acute abdominal pain. Earlier diagnosis may be enabled with the plain abdominal X-rays and transabdominal ultrasound. There are an approximately equal number of these perforations developed after Cesarean section (CS) and vaginal delivery (Table 4.3). After CS, these perforations occur during the first several days of puerperium (Table 4.3). In the immediate postoperative period, abdominal symptoms may be interpreted as constitutional symptoms emanating from pregnancy or surgery [125]. Often a presumptive diagnosis of paralytic ileus is made and in some instances that of puerperal sepsis, which

Table 4.3 Published cases of perforated peptic ulcers during puerperium

Study	Age	Days after delivery	Ulcer type	Duration (h)	Operation	Mother/birth	Child
Anderson, 1942 [90]	29	4 h	Duodenum	48	No	Died/vaginal	Live
McGarvey, 1952 [130]	41	2	Duodenum				
Ross, 1958 [105]	28	1	Duodenum, anterior	60		Live/vaginal	Live
Jones, 1969 [125]	42	4	Duodenum	72	Abdominal drainage	Live/vaginal	Live
Parry, 1974 [131]			Duodenum				
Munro, 1975 [124]	42	4	Prepyloric	70	Sutures	Vaginal	
Kaczmarek, 1970 [132]						C-section	
Opitz, 1971 [128]			Gastric				
Gaĭstruk, 1980 [127]			Gastric				
Uchikova, 2004 [133]			Duodenum			C-section	
Engemise, 2009 [98]	29		Duodenum, anterior	50	Omental patch	Live/C-section	Live
Alabi-Isama, 2009 [134]							
Sule, 2010 [135]	25	3	Duodenum, anterior	7 days	Omental patch	Live/C-section	Live
Nazir, 2013 [136]	24	3	Duodenum, anterior	5 days	Omental patch	Live/vaginal	
Miles Dua, 2012 [137]	23	2	Duodenum, anterior	4 days	Omental patch	Live/vaginal	Live
Maruyama, 2016 [138]	33	13	Duodenum	48	Sutures	Live/C-section	Live
Chekan, 2016							
Nikhat, 2017 [139]	21	6	Duodenum, anterior	24	Omental patch	Live/C-section	Live

could result in a relaxed approach in dealing with such symptoms.

After vaginal delivery, half of the patients were older than 40 years [124–126] and another half less than 29 [90, 105]. In this group, PPU also developed during first days after delivery. There were two reports of gastric perforation [127, 128], but most of the medical data were not available (Table 4.3).

There are several diagnostic problems in the puerperium. Nonspecific abdominal pain is experienced by 98% and 92% of primiparous and multiparous women, respectively [129]. Another fact is that about 60% of all postlaparotomy patients will have evidence of pneumoperitoneum, and this will take 1–24 days to be absorbed. This is important for patients with abdominal pain after CS making the diagnosis more difficult. In such cases, water-soluble contrast swallow will show a free peritoneal leak. The absence of peritoneal irritation in the puerperium must be stressed, since failure to recognize this may result in a serious delay in establishing a diagnosis [105].

4.1.2.4 Diagnosis

The only role radiology would have in the pregnant patient with PUD is confirmation of perforation. The usual approach to the diagnosis of pneumoperitoneum is to perform plain abdominal X-rays [120]. The upright lateral chest radiograph confirms pneumoperitoneum in 98% of the cases. This is more sensitive than the upright posteroanterior chest radiograph, which shows the pneumoperitoneum in 80% of the cases [140]. The performance of a lateral chest radiograph excludes the fetus from the direct beam; if negative for the presence of free intraperitoneal air, this would support more conservative management. In the presence of strong clinical suspicion for intra-

abdominal disease, the decision to perform further imaging, such as abdominal CT, versus surgical exploration will have to be made on an individual basis.

4.1.2.5 Treatment

The treatment of PPU consists of surgical intervention and perioperative pharmacological gastric acid suppression.

Surgical Treatment

In the first half of the twentieth century, there were cases of PPU in pregnancy treated conservatively. In 1943, Sandweiss et al. stated "When indications are present, pregnancy or puerperium should not be considered as a contraindication to surgical therapy" [13]. Only 24 cases of PPUs have been described up to 1966 [13, 14, 17, 27, 42, 90, 105–111]. In that series 16 patients (67%) were treated medically (nasogastric suction, nil by mouth, and antibiotics when available) with 16 maternal and 11 infant deaths. As in nonpregnant population, conservative therapy of PPU is not an acceptable option. James first recorded successful suture of a duodenal ulcer perforation [27]. Omental patch repair with *H. pylori* eradication (if present) is the standard of care for sealing duodenal perforations and preventing reperforations. Postoperative complications such as intra-abdominal abscess [135] should be drained as soon as possible. If the adjustable gastric band is the cause of the marginal or peptic ulcer, it should be removed during emergency operation [113]. Burkitt described the first emergency partial gastrectomy for a large duodenal ulcer perforation occurring at the 31st week [106]. First partial gastrectomy for massive bleeding peptic ulcer was performed by Vasicka in 1957 (see Chap. 4).

Perioperative Gastric Acid Suppression

Histamine$_2$ Receptor Antagonists (H$_2$RA)

The H$_2$RAs are the most commonly used and safest medications for the pregnant woman with heartburn not responding to lifestyle modification and nonabsorbable medication. All four drugs (cimetidine, ranitidine, famotidine, and nizatidine) are FDA category B.

Cimetidine and ranitidine. Cimetidine and ranitidine have had considerable use in pregnancy over the last 30 years with an excellent safety profile. Only ranitidine's efficacy has been specifically studied during pregnancy for heartburn [141]. No adverse pregnancy outcomes or drug reactions were noted. Cimetidine has a weak antiandrogenic effect in animals [142], while ranitidine has no antiandrogenic activity in animals [69]. Neither H$_2$RA has reports of human sexual defects in infants. To date, the safety of cimetidine and ranitidine has been assessed in over 2000 pregnancies in database studies not sponsored by the manufacturers. In the surveillance study of 229,101 pregnancies in the Michigan Medicaid recipients between 1985 and 1992, a similar rate of major birth defects was detected (4.3% with cimetidine, 4.5% with ranitidine, and 4.3% in women taking no medications during their pregnancies) [143]. In summary, cimetidine and ranitidine have not been associated with an increased risk of congenital malformations [144–146] Ranitidine is the only H$_2$RA with documented efficacy in pregnancy.

Famotidine and nizatidine. There are much less reported safety data with these latter H$_2$RAs than cimetidine and ranitidine. Pregnant rabbits with the equivalent of 300 times the recommended human dose of nizatidine encountered abortions, low fetal weights, and fewer live fetuses [147]. On the contrary, rat studies found no adverse effects on the fetal pups [148]. In the Michigan Medicaid Surveillance Study, 6.1% of fetuses exposed to famotidine during the first trimester of pregnancy developed major birth defects compared with the expected prevalence of one [143]. The small size was too small to draw firm conclusions, however. With nizatidine, there is only one case of a woman delivering a healthy baby after taking the drug during 14–16 weeks of gestation. Although few reports are available, famotidine appears safe during pregnancy. Although nizatidine was previously classified as FDA category C, the FDA recently reclassified it as a category B drug. However,

the conflicting animal data are troublesome and suggest that other H_2RAs may be safer during pregnancy. The PPIs are the most effective drug therapy for symptom control and healing of esophagitis. The PPIs have not been as extensively used in pregnancy as the H_2RAs or is their efficacy proven in pregnancy, and the data about total safety are more limited.

Proton-Pump Inhibitors (PPIs)

Omeprazole. The first of the PPIs is classified as an FDA category C because, at doses similar to those used in humans, omeprazole produced dose-related embryonic and fetal mortality in pregnant rats and rabbits [149]. No teratogenicity was observed. The FDA has received reports of at least 12 birth defects in pregnant women exposed to omeprazole, including anencephaly and hydroencephaly [143]. However, other case reports and small case series have found no infant congenital malformations in mothers taking 20–60 mg omeprazole/day, even in the first trimester of pregnancy [150]. A meta-analysis showed the relative risk for all major malformations among any PPI exposure of 1.18, a nonsignificant relative risk [151]. For the four studies where data for only omeprazole could be extracted, the relative risk was 1.05, also indicating a nonsignificant relative risk of malformations. Although the weight of evidence suggests omeprazole is safe in pregnancy, the FDA has not changed its class C rating.

Lansoprazole. Animal studies using doses of lansoprazole up to 40 times the recommended human dose have found no evidence of impaired fertility or fetal toxicity. Human data on the safety of lansoprazole in pregnancy are more limited. In one nonobservational cohort study [150], six pregnant patients taking lansoprazole during the first trimester delivered seven healthy newborns. Lansoprazole was the only acid-suppressing drug exposed in 13 infants reported to the Swedish Medical Birth Registry [146]. Two birth defects were observed: one atrial septal defect and one undescended testis. In a Danish study from 1999, 38 patients had taken PPIs during the first trimester of pregnancy (35 omeprazole, 3 lansoprazole) [152]. The prevalence of major birth defects, low birth weight, and prematurity was no different than in pregnant controls not receiving any medications. In another study, the rate of congenital abnormalities did not differ between the exposed and control groups: omeprazole 3.6%, lansoprazole 3.9%, and pantoprazole 2.1% versus controls 3.8%. No differences were found when exposure was limited to the first trimester [153]. The lack of teratogenicity in animals is reassuring, accounting for the FDA category C for lansoprazole use during pregnancy. However, the data on safety in human pregnancies are limited, and avoidance of this PPI and all PPIs, especially during the first trimester, is the safest course. If lansoprazole is required or if inadvertent exposure occurs early in gestation, the fetal risk seems to be low. Based on product information from the individual manufacturers, the newer PPIs (rabeprazole, pantoprazole, and esomeprazole) have been shown safe in various animal studies. No reports describing the use of these newer PPIs during human pregnancies are available [143]. PPIs should only be used during pregnancy in women with well-defined complicated GERD, not responding to lifestyle changes, antacids, and H_2RAs.

Gastric Acid Suppression During Lactation

All systemic antireflux medications are excreted in breast milk and could harm the infant. Therapeutic options must be explained and discussed with women who require treatment but who want to breastfeed. Drug safety during lactation has been assessed in animal studies and human case reports (Table 4.4).

Antacids

Aluminum and magnesium hydroxide antacids are not concentrated in breast milk and, thus, are safe during lactation. Neither Gaviscon nor sucralfate has been studied during lactation but is presumed safe because of limited maternal absorption.

Histamine$_2$ Receptor Antagonists

All H_2RAs are excreted in human breast milk. Cimetidine and ranitidine reach concentrations in breast milk 4–7 times the doses present in maternal serum [154]. In contrast, famotidine only reaches a mean milk to plasma concentration of

Table 4.4 Safety of antiulcer/GERD medications during lactation

Medications	Safety	Comments
Antacids	Yes	Not concentrated in breast milk
Sucralfate	Yes	Minimal, if any, excretion in breast milk
Cimetidine	Yes	Compatible with breastfeeding (*American Academy of Pediatrics*)
Ranitidine	Yes	Excreted in breast milk in concentrations similar to cimetidine
Famotidine	Yes	Lowest concentrations in breast milk of all H_2RAs
Nizatidine	No	Growth depression in pups of lactating rats
PPIs	No	Growth depression in pups of lactating rats

GERD gastroesophageal reflux disease, *H_2RA* histamine$_2$ receptor antagonist, *PPI* proton-pump inhibitor

1.78, 6 h after ingestions [155]. Small amounts of nizatidine are excreted into human breast milk [156]. In the animal studies assessing H_2RA safety during lactation, pups reared by lactating rats ingesting nizatidine experienced growth retardation [157]. The effects of H_2RAs in breast milk on the nursing human infant are unknown. In 1994, the *American Academy of Pediatrics* classified cimetidine as compatible with breastfeeding [158]. Others also suggest that ranitidine and famotidine are safe, and the latter H_2RA may be preferred because of the lower concentration in human breast milk. Nizatidine should be avoided in the breastfeeding mother because of the single animal study [157].

Proton-Pump Inhibitors

Little is known about PPI excretion in breast milk or infant safety in lactating women. PPIs probably are excreted in human milk, because of their relatively low molecular weight. This was confirmed in the only report of PPI use during breastfeeding [159]. During the day, the patient fed her infant son just before taking omeprazole at 8:00 am, refraining from nursing for 4 h, and then expressed and discarded her breast milk at noon. At 3 weeks postpartum, blood and milk samples were obtained at 8:00 am and then every 30 min for 4 h. Breast milk levels of omeprazole began to rise at 9:30 am and peaked at 11:00 am at 58 mm, considerably lower value than simultaneous maternal level of 950 mm. The infant was doing well at 1 year. However, rats administered with omeprazole at 35–345 times and rabeprazole at a dose of 195 times the recommended human dose during late pregnancy and lactation had decreased body weight gain of their pups [149]. Therefore, PPIs are not recommended for use by lactating mothers. Women can either take PPIs and discontinue nursing or use medications (i.e., H_2RA) from another class.

4.1.2.6 Prognosis

The diagnosis is often made late in pregnancy with quite devastating consequences. In the series of 24 cases described up to 1966, 16 patients were treated medically with 16 maternal (maternal mortality 100%) and 11 infant deaths (fetal mortality of 69%), while 8 patients received surgical treatment (7 simple closures and 1 partial gastrectomy) without maternal and 2 infant deaths (of the 2 infants who died, 1 was a twin, the other twin survived), making fetal mortality 29% [13, 14, 17, 27, 42, 90, 105–111]. It is questionable how Paul et al. in 1976 found only six cases of maternal survival following PPU and, of these, only four were associated with survival of both the mother (maternal mortality 33%) and infant [114]. Early surgical diagnosis and treatment followed by vaginal delivery at term offer the best chance for survival of the mother and child.

Table 4.2 shows cases during pregnancy (without puerperium) with maternal data of 18 mothers. The survival rate today is approaching 100%. Table 4.3 shows also 18 cases of PPU during puerperium, but the data about the maternal and fetal outcome are lacking; therefore, the maternal prognosis cannot be made accurately, but it seems that it is similar to the pregnant group.

4.2 Perforated Malignant Peptic Ulcer/Carcinoma

Perforated gastric carcinoma is an extremely rare condition due to the rarity of gastric cancer in the pregnant population. The characteristics of gas-

tric cancer in young (pregnant) women are discussed for easier understanding and diagnosis of such condition during pregnancy.

4.2.1 Gastric Cancer in Pregnancy

4.2.1.1 Incidence

Only 0.4–0.5% of gastric cancers occur in women aged less than 30 years [160]. The incidence of gastric cancer associated with pregnancy is comparatively low, found in 0.026–0.1% of all pregnancies [161, 162]. It was first reported by Fujimura and Fukunda in 1916 [163]. In the period from 1969 to 1999, a total of 31 cases of pregnancy-associated gastric cancer has been published [164], with subsequent sporadic reports. On the other hand, owing in part to the relatively high incidence of gastric cancer in Japan, more than 100 cases have been reported in this country up to 1987 [161]. The largest study from Japan accumulated 137 patients adding to Ueo et al. [161] another 37 cases of pregnancy-associated gastric cancer that had been newly reported in Japan from 1988 to 2007: these consisted of 2 cases in 1968–1977, 6 cases in 1978–1987, and 29 cases in 1987–2007 [165–167].

Krukenberg Tumor

The association of Krukenberg tumor and pregnancy is extremely rare. For over a century and its first description in 1896 by Krukenberg [168], literature search documented around 50 cases during pregnancy (Table 4.5). The reported incidence of Krukenberg tumor with a primary gastric carcinoma in pregnancy is 2.6% (3/112) [169]. The rarity of this disease is due to the rarity of gastric cancer in young women. Incidence in future decades cannot be estimated. On one hand, with increasing childbearing of women over 30 years, increasing incidence could be expected, but, on the other hand, the incidence of (advanced) gastric cancer is declining in Western countries.

Table 4.5 Review of reported cases of Krukenberg tumor in pregnancy with a primary gastric carcinoma

Symptoms	Total number of reported cases (n = 50)
Epigastric pain, nausea and vomiting, bloating	42
Maternal virilization (rapid onset)	05
Rapid increase in abdominal girth	03
Diagnostic criteria	
Signet ring morphology	50
Supportive findings	
Mucin positivity	09
Raised CEA	03
Raised CA-125	05
CK7/CK20 positivity	03
Radiology (ultrasound/CT scan)	38
Outcome	
Healthy fetus	49
Fetal demise	01
Maternal outcome (average survival) (months)	6–12
Decision	Delivery of baby
	Platinum-based chemotherapy
	Salpingo-oophorectomy and gastrectomy in resectable tumor

CEA carcinoembryonic antigen, *CA* cancer antigen, *CT* computed tomography, *CK7* cytokeratin 7, *CK20* cytokeratin 20
Reproduced with permission from [170]

4.2.1.2 Pathology

Pathology according to the largest review from Japan shows that diffuse type is more common (86.9%) than the intestinal type (13.1%) [165]. While in older patients the majority of carcinomas are of the intestinal, usually well-differentiated type, the tumors in young patients are mainly poorly differentiated carcinomas of the diffuse type with signet ring cells and peritoneal metastasis.

4.2.1.3 Pathophysiology

The literature on gastric cancer in the young adults has described almost similar findings: the female dominance with a male to female ratio of 1:1.5 [171], more aggressive histological features, the advanced disease stage at presentation, and the poorer prognosis [172]. These character-

istics were even more pronounced in the pregnancy-associated cases [162, 173]. Being more common in females, the association of gastric cancer and pregnancy could be purely a natural coincidence, but it has been postulated that the immunosuppression during pregnancy is conducive for tumor growth and the biological and hormonal circumstances further enhance tumor progression [173, 174]. A suppressive effect of sex hormones on spreading of stomach cancer in a rat model was demonstrated [174]. Placenta secretes histaminase which degrades histamine function; hence, the patient shows no deterioration of symptoms caused by the cancerous ulcer. As it is known, blood circulation increases during pregnancy; pregnant women are particularly susceptible to the rapid growth and spread of cancer.

4.2.1.4 Clinical Presentation

Perforated Malignant Ulcer

The presentation is the same as classic peptic ulcer perforation (see Sect. 4.1.2.3).

Krukenberg Tumor

A maternal and fetal virilization can be observed [175]. This virilization, nonspecific to Krukenberg, is due to luteinized ovarian stroma reaction, stimulated by the placental production of steroids and human chorionic gonadotropin. The pelvic mass was found in 49.3% of cases [169]. Its management during pregnancy is difficult. Indeed, the incidence of malignant tumors is only about 1–6% of adnexal masses associated with the pregnancy. The differential diagnosis with luteomas or other benign adnexal pathology, where the management is radically different, is not always easy.

4.2.1.5 Diagnosis

Hormonal and immunosuppressive effects of pregnancy could explain why most cases of gastric cancer associated with pregnancy are usually advanced by the time that they are diagnosed. Misdiagnosis is another contributing factor as the symptoms are frequently masked by factors related to the normal pregnancy. Sometimes the symptoms are mingled and masked by the hyperemesis gravidarum. Sometimes, symptoms are attributed to the pregnancy and not evaluated further until delivery or complications develop [162, 173]. Detection can be further delayed as therapeutic approaches will usually be restricted with the physical and psychological clinical events surrounding the pregnancy. Diagnostic modality for definitive diagnosis as in nonpregnant patients is esophagogastroduodenoscopy (EGD). Indications for the repeated EGD are the same as in nonpregnant patients. It is confirmed by the fact that a patient with an exacerbation of PUD presented with gastric carcinoma during pregnancy [176].

In pregnant patient, MRI is preferred to CT scan due to the ionizing radiation. Although not specific, the presence of solid components showing hypo-intensity on T2-weighted images in an ovarian mass appears to be a characteristic finding of Krukenberg tumors (Figs. 4.4 and 4.5), especially if the tumors are bilateral, have sharp margin, are thin walled, and have an oval config-

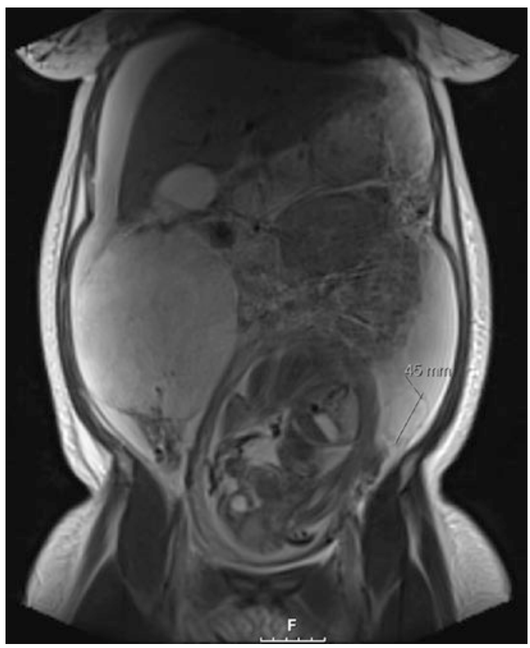

Fig. 4.4 Coronal T2-weighted MR image revealing a 29-week gravid uterus with well-defined bilateral ovarian masses and extensive free fluid in the abdomen and pelvis. Reproduced from [179] under the CC BY 3.0

Fig. 4.5 Axial T2-weighted MR image revealing bilateral Krukenberg tumors. Both are well encapsulated and have oval form. Reproduced with permission from [178]

uration [177, 178]. Except for primary tumor, the metastatic form can be found, which can sometimes, as when Krukenberg tumor is present, mislead the clinician to the diagnosis of the primary ovarian tumor during pregnancy. Therefore, the definitive diagnosis is histological, marked by areas of mucoid degeneration and by the presence of signet ring cells.

4.2.1.6 Treatment

Primary Gastric Tumor

Because of this as well as the fact that the peritoneal cavity will already be contaminated by cancer cells, surgery should be as palliative as possible. In view of the poor outcome, a simple closure of the perforation or omentopexy is the usual procedure.

Metastatic Tumor

Indication for the palliative or curative surgery is the same as in general population. Concerning Krukenberg tumor, aggressive surgery can improve the prognosis; but its management depends essentially on the findings at laparotomy and duration of pregnancy. If no other metastatic disease except involvement of both ovaries is found (Fig. 4.6), bilateral oophorectomy with or without hysterectomy can be performed. The decision on the termination of pregnancy depends on the trimester of pregnancy and patient's decision about current pregnancy. If the diagnosis of primary gastric carcinoma is known before the operation, the definitive operation can be done in the same act. If the primary tumor is not known, the diagnostic workup should be done and the indications for the operation made according to the stage of the primary gastric carcinoma.

Fig. 4.6 Bilateral Krukenberg tumor at 10-week pregnancy without other metastatic disease found at laparotomy. Reproduced with permission from [178]

Cesarean Section

With regard to the fetus, an induced delivery or early CS will simplify management of the mother provided the fetus has reached viability. Otherwise, an abortion is not known to be therapeutic, and an early pregnancy can be left undisturbed unless irradiation or chemotherapy is planned.

Hormonal Therapy

The effect of estrogen and the results of antiestrogen treatment in clinical trials are controversial. The largest non-Japanese review reported that the features and prognosis in gastric cancer associated with pregnancy were the same as in nonpregnant young patients [164].

4.2.1.7 Prognosis

Maternal Outcome

Pregnancy-associated gastric cancer is found in the advanced, metastatic stage in 95.5% of the patients, and only 44% of the patients underwent surgical resection [161]. Krukenberg tumors with

a primary in the stomach carry a more daunting prognosis in pregnancy due to the presence of estrogen receptors in a high proportion of gastric carcinoma leading to an aggressive behavior [179]. Therefore, the prognosis is extremely poor, i.e., 1-year survival of 14.5–18% and 2-year survival of 10.6–15% [161, 165, 170]. Another 30-year review found 100 reports of pregnancy-associated gastric cancer and only one survivor was detected. Maternal survival of 9–19 months after diagnosis in pregnancy was observed for all other cases [180]. Even in regard to the 27 patients diagnosed in the most recent 20 years, the 1- and 2-year survival rates were 37% and 32%, respectively [165]. In conclusion, the prognosis of patients with pregnancy-associated gastric cancer remains poor, although it seems to be somewhat improved compared with the previous large report [161].

Fetal Outcome

There is no significant impact on fetal survival as most (97%) of the reported cases have led to the delivery of the healthy baby [170].

4.2.2 Perforated Gastric Cancer in Pregnancy

4.2.2.1 Incidence

There are four cases of perforated gastric cancer during pregnancy published with extremely poor prognosis. One is a 29-year-old woman from Turkey [181] and three others from Japan, one during CS [182], another during pregnancy during workup for ovarian tumor [183], and the third during delivery with misdiagnosed placental abruption [184]. There is only one case of perforated malignant ulcer in a 43-year-old 17th gravid patient, who developed a perforation of a carcinomatous ulcer of the stomach on the 8th day of puerperium [185].

4.2.2.2 Treatment

Primary Gastric Tumor

The difference between benign and malignant ulcer or carcinoma is the necessity of oncologic curative or palliative surgery. If perforated carcinoma is found during CS, definitive oncologic surgery could be made or just suturing as the therapy for the perforation and another exploration is made for definitive surgery. If the perforation is found during pregnancy, further therapy depends on the stage of pregnancy as in other malignant tumors during pregnancy. In early pregnancy termination of pregnancy with oncologic surgery is made. In advanced pregnancy, oncologic surgery can be postponed after delivery, or if pregnancy is around the 27th week, then corticosteroids are used for fetal lung maturation and CS with definitive surgery is made.

Because of this as well as the fact that the peritoneal cavity will already be contaminated by cancer cells, surgery should be as palliative as possible. In view of the poor outcome, a simple closure of the perforation or omentopexy is the usual procedure.

4.2.2.3 Prognosis

One patient died 6 months after initial diagnosis of gastric cancer despite surgical therapy and adjuvant chemotherapy [181]. Unfortunately, the data for three Japanese cases [182–184], as well as for perforated malignant ulcer [185], were not available.

4.3 Nonpeptic Ulcer Perforations/Ruptures

4.3.1 Spontaneous Gastric Rupture

4.3.1.1 Historical Perspective and Incidence

Spontaneous rupture of the stomach in general population was the subject of medical speculation as long ago as 1819, but Carson's report in 1846 offered the first proof of its occurrence in humans [186]. Glassman in 1929 collected 14 cases of nontraumatic rupture of the stomach from the literature and noted that there was but one survival [187]. Miller has made the first report of *spontaneous rupture* of the stomach during labor or the postpartum period [188]. It is an extremely rare condition with around ten cases published [188–191].

4.3.1.2 Etiopathogenesis

Spontaneous gastric rupture is rare because the stomach is anatomically protected in the upper abdomen by the liver and ribs and because the stomach has mobile distensible walls and two valves, gastroesophageal and pyloric, to decrease intragastric pressure.

It is apparent from the reports of *spontaneous rupture* of the stomach or intestine that distention of the viscera invariably precedes rupture. Acute gastric dilatation is a recognized complication of the postpartum period which is most frequently of functional origin. Pylorospasm, “dropping” of the stomach and intestines to their antepartum position, hypotonicity of the bowel, and “nutritional edema” of the pylorus have also been suggested as etiological factors in acute postpartum gastric dilatation. Gastric dilatation and intestinal ileus are prone to occur after abdominal operations and especially when peritonitis is present. Whatever the cause of the dilatation, sustained distention of the stomach may lead to an ischemic necrosis of the mucosa with disruption of this layer and subsequent extension through the remainder of the stomach wall [188, 192]. Nontraumatic rupture of the dilated stomach occurs most frequently near the lesser curvature and explains this predilection by the external fixation of the lesser curvature and the reduced “elastic coefficient” of the “magenstrasse” [192, 193]. These authors describe a symptomatic triad of:

- Tympanitic distention of the abdomen
- Subcutaneous emphysema
- Shock

The first factor leading to increased intragastric pressure is dilatation of its walls following sudden consumption of large quantities of food. Historical studies on cadavers by Revilliod in 1885 indicate that the stomach has enormous capacity. Gastric rupture due to overfilling could occur only after a rapid filling of a stomach with 4 L of fluid and that the rents occurred in midstomach, both anterior and posterior walls [194]. Key Aberg in 1897 made the experiment in sitting position and found that filling with 4 L made ruptures on the lesser curvature. Vomiting is a significant contributing factor in Mallory-Weiss syndrome, causing longitudinal cracks in the gastric mucosa near the cardia. The abovementioned cracks may penetrate into the muscular layer. Sometimes vomiting may lead to the rupture of the distal esophagus (Boerhaave syndrome). The difference is that the esophageal rupture occurs during vomiting with gastric contents, while gastric rupture occurs during nausea and vomiting reflexes. Pathogenesis of gastric rupture sometimes involves arterial ischemia of the gastric wall despite its excellent blood supply. Inflammation of the gastric mucosa is also a significant factor. Trauma, e.g., indirect cardiac massage or chest thump, is also causative [195]. High position of the diaphragm intensifies activity of the valve closing the gastric cardia. Compression of the stomach by the uterine fundus increases intragastric pressure and impairs gastric emptying. The probable inflammation of the gastric mucosa decreases the resistance of its walls.

The pathologically dilated stomach becomes susceptible to rupture during forceful emesis when an abrupt increase in intra-abdominal pressure occurs [196]. Once the stomach becomes critically dilated, the lower esophageal sphincter functionally becomes a one-way valve, allowing contents to only enter into the stomach. Such gastric ruptures typically occur on the lesser curvature where the stomach is less elastic. Important is the rapidity of onset and depth of the shock, and note that these patients die in the first 9–10 h without alleviation of the state of shock by vigorous, supportive treatment.

Christoph and Pinkhamew in 1961 believed that the pathogenesis of the gastric rupture has a definite sequence in a peritonitis [189]. Because of the stress from perforation of the appendix and peritonitis, which may have spread following involution of the uterus, and spontaneous delivery, the basis for acute gastric dilatation was present. The distention was sufficient to cause ischemic necrosis of the gastric mucosa [188, 197] with a subsequent tearing of the outer layers of the stomach wall by the trauma of persistent emesis. Because of the surgical vent in the

right-lower quadrant, this case did not demonstrate the tympany and subcutaneous emphysema described by others [197]. In view of the facts that postpartum gastric dilatation and postoperative abdominal distention are frequent complications without causing "unexpected rupture" of a viscus, an additional factor must have had a vital role in the present case. Christoph and Pinkhamew in 1961 believed that stress and chemical imbalance from her several difficulties may have produced changes in the gastric mucosa similar to those produced in major burns [189]. It seems probable that the subtly damaged gastric wall was thus more susceptible to ischemic necrosis and subsequent rupture than the normal stomach. Some authors believe that the term "spontaneous rupture" of the stomach is a misnomer and that "unexpected rupture" is a more descriptive phrase [189, 192]. In reviewing the available reports of so-called spontaneous rupture of the stomach, a pathologic basis, whether it was ulcer, carcinoma, or gastric dilatation of undetermined cause, was demonstrated at operation or at postmortem examination in all cases. It should be noted that both cases of gastric rupture in pregnancy were located on the greater curvature [188, 190].

4.3.1.3 Prognosis

Previous literature indicated high maternal and newborn mortality. There is one case with maternal survival but fetal death in 2002 [190]. The key for maternal survival was early suspicion and diagnosis, early aggressive resuscitation, and emergency laparotomy.

4.3.2 Postoperative Gastric Perforation/Rupture

4.3.2.1 Gastric Ulcer Perforation

Post-gastric Banding

The laparoscopic placing of an inflating silicon band around the stomach and reducing its orifice, also known as gastric banding, is a surgical procedure that reduces maternal obesity. This procedure is associated with increased unplanned pregnancies. The most common effect reported during pregnancy is repeated/intractable nausea and vomiting, resolving with deflating of the silicon band. This complication imposes a diagnostic dilemma as to whether bowel obstruction or other intra-abdominal pathologies are involved.

A *marginal ulcer* is a known complication of bariatric surgery and is a result of tissue ischemia caused by reduced blood supply to the stomach because of the inflated ring [198]. Therefore, when the patient deteriorates under conservative management and a laparotomy is performed, removal of the ring is necessary to resume appropriate gastric blood supply, which is important for a proper gastric healing. Weiss et al. reviewed the results of seven pregnancies, five of which had progressed to delivery [199]. All bands were decompressed because of nausea and vomiting, and two patients had serious complications: one had an intragastric migration of the band and the other a balloon defect. Both had to be operated on to remove the band. Laparoscopic gastric banding is considered an efficient and relatively safe procedure for the treatment of maternal obesity. The severely obese pregnant patients with previous gastrointestinal surgery demonstrate one of the unique management dilemmas when presenting with intractable vomiting. This case is even more complicated because a combination of other clinical symptoms suggesting preeclampsia and fetal distress, on top of obesity and vomiting, made the diagnosis even more difficult [113].

4.3.2.2 Gastric Rupture Caused by Diaphragmatic Hernia

See Chap. 6.

4.4 Intestinal Perforation

If intestinal obstruction with perforation and inflammatory bowel diseases are excluded (see Chaps. 7 and 8), small and large bowel perforation is extremely rare during pregnancy. The most common causes are intestinal endometriosis, colorectal carcinoma, instrumental abortion, and spontaneous or idiopathic perforation.

4.4.1 Intestinal Endometriosis

4.4.1.1 Introduction

Endometriosis is defined by the presence of endometrium outside the uterus and usually affects pelvic structures including the bowel. Intestinal involvement occurs in 5–12% [200] of patients with endometriosis. The most frequent location is the sigmoid colon, followed by the rectum, ileum, appendix, and cecum [201]. The peritoneal implantation of endometrium by retrograde menstruation or the possible metaplasia of peritoneal cells is still the most accepted etiological theory of endometriosis. Intestinal endometriosis may be found in every layer of the bowel wall, but it is most commonly found within the subserosa as superficial serosal implants [202, 203]. *Deep bowel endometriosis* is defined as a solid mass situated deeper than 5 mm under the peritoneum [204]. Under cyclical hormonal influences, these implants may proliferate and infiltrate the intestinal wall and cause a fibrotic reaction with formation of strictures and adhesions, which may lead to bowel obstruction and recurrent abdominal pain [205, 206]. On the other hand, transmural bowel wall involvement is not so common, and the intestinal mucosa usually remains intact, and perforation of the affected intestinal tract is a very rare complication [203, 207].

4.4.1.2 Incidence

Endometriosis causes lower fertility rates. Fortunately, due to assisted reproductive techniques, these patients have good chances to become pregnant even if endometriosis is not completely removed. The result is the possible higher incidence of endometriosis-related complications during pregnancy. One of these is bowel perforation due to retained bowel endometriosis. The additional problem could be the influence of IVF on endometriosis recurrence rate of 7% at 12–21 months after IVF [208, 209]. Others studies, fortunately, did not confirm these results but this topic should be kept in mind [210, 211].

Up to 2016, less than 30 cases [212, 213] of intestinal perforation (appendiceal perforation excluded, see Chap. 1) from endometriosis have been reported, and among these, around 50% occurred in pregnancy and puerperium (Table 4.6). Of these 11 patients, almost all presented in the third trimester or puerperium. Patients with endometriosis-induced perforated acute appendicitis (about 20 cases published) were excluded and analyzed separately (see Chap. 1) due to the presentation as acute appendicitis.

One of postpartally presenting patients with cecal perforation had a past medical history of terminal ileal and cecal Crohn's disease diagnosed 9 years previously, but histology confirmed decidualized endometriosis without evidence of Crohn's disease [214].

> The sigmoid colon is the most common site of perforation from endometriosis in general and pregnant population accounting for more than 50% of published cases in pregnancy (Table 4.6) [214, 215].

4.4.1.3 Pathophysiology

Preexisting endometriosis-derived ectopic decidua is very similar to de novo ectopic decidua. A past history of endometriosis and the

Table 4.6 Bowel perforation sites secondary to endometriosis during pregnancy and postpartum (without appendix)

Author	Year	Perforation site	Pregnancy duration
Haufler [216]	1931	Jejunum	6 months
Nishikawa et al. [217]	2013	Ileum	33 weeks
Albareda et al. [213]	2016	Ileum	Postpartum (5 months)
Beamish et al. [214]	2010	Cecum	Postpartum
Clement [218]	1977	Sigmoid	37 weeks
Rud [219]	1979	Sigmoid	
Floberg et al. [220]	1984	Sigmoid	Postpartum (41 weeks)
Loverro et al. [276]	1999	Sigmoid	35 weeks
Schweitzer et al. [205]	2006	Sigmoid	40 weeks
Costa et al. [212]	2014	Sigmoid + Rectum	25 weeks
Pisanu et al. [215]	2010	Rectum	33 weeks

presence of glandular endometrial structures can aid in differentiation. De novo ectopic decidua is usually asymptomatic and found incidentally during CS, mostly on ovarian surfaces or the uterine serosa. Endometrial glands with decidualized stroma are observed in the submucosa suggesting that the pathogenesis of ectopic decidua was due to preexisting endometriosis.

In the third trimester and postpartum, endometrial lesions tend to contract as observed by McArthur and Ulfelder, the mechanism of which remains obscure. This contraction in an area already weakened by endometrial stromal infiltration can cause perforation [202, 221]. In those patients with perforation, the entire intestinal wall is replaced by endometriotic tissue (Fig. 4.7). In pregnancy, under the effect of progesterone, the area of ectopic endometrium becomes decidualized with a progressive reduction in size [221, 222]. Actually, the reduction in size of a transmural endometriotic nodule may lead to perforation, by weakening of the intestinal wall [202], particularly in the third trimester, which is the time of perforation in most reported cases [202, 215, 221]. Moreover, decidualization causes a severe inflammatory response with an increased number of natural killer cells and decidual changes, which are responsible for a higher risk of perforation [222, 223]. Additionally perforation can also be facilitated by the progressive traction of the enlarged uterus on the strictly adherent surrounding bowel loops and, consequently, on the decidualized and weakened area of the bowel wall [215]. Moreover, constipation is common in pregnancy, so the intestinal stenosis due to endometriosis may cause an increase in intra-intestinal pressure and subsequent intestinal perforation. Although endometriosis improves during pregnancy, the cases described show the potential occurrence of serious and unexpected complications of the disease.

4.4.1.4 Clinical Presentation

Intestinal endometriosis typically takes the form of asymptomatic serosal implants that occasionally result in (partial) intestinal obstruction with recurrent abdominal pain [202]. Transmural involvement is not as common, and spontaneous perforation of transmural intestinal endometriosis is rare (Table 4.6).

If the perforation is present, the symptoms and signs of the acute abdomen are present. Before the occurrence of perforation, abdominal pain could be cyclical as is present in endometriosis. Location of pain depends on the part of the intestine infiltrated with endometriotic nodule(s). Therefore if the appendix vermiformis is involved, acute appendicitis is a classic presentation (see Chap. 1). In some cases, the duration of pain before the perforation can be several weeks [217]. Larger nodules infiltrating the intestinal muscular layer cause a wide range of symptoms

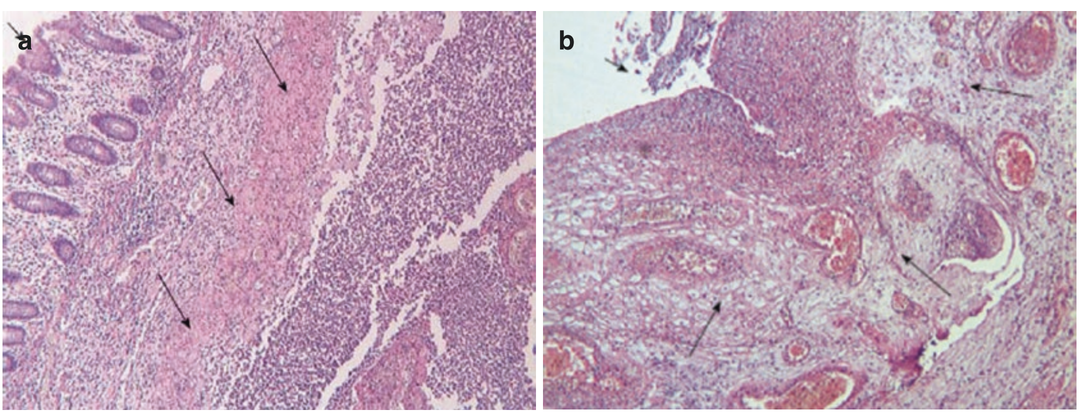

Fig. 4.7 The rectal wall. (**a**) Decidualization of the rectal wall (*long arrows*), mucosa side of the rectal wall (*short arrow*) (HE, ×40). (**b**) Decidualized endometriosis around the rectal perforation (*long arrows*), rectal perforation with necrosis at the peritoneal side of the rectal wall (*short arrow*) (HE, ×100). Reproduced with permission from [215]

including dyschezia, constipation, diarrhea, abdominal bloating, painful bowel movements, the passage of mucus in the stools, and cyclical rectal bleeding [224, 225]. The symptoms associated with intestinal endometriosis often mimic diarrhea-predominant or constipation-predominant irritable bowel syndrome [226]. Enlargement of endometriotic nodules could aggravate constipation or initiate abdominal distention due to impaired bowel peristalsis. Also, due to transmural involvement, the patient can present with GI hemorrhage prior to or with the perforation itself.

4.4.1.5 Differential Diagnosis

Before intestinal perforation occurs and due to a wide range of symptoms, differential diagnosis may be particularly challenging. Both the rareness of the perforation and the symptoms that are suggestive of pyelonephritis or diverticulitis may be misleading and could delay the diagnosis especially before the perforation ensue.

4.4.1.6 Diagnosis

If the acute abdomen is suspected or confirmed on clinical grounds, standard laboratory investigations and plain abdominal X-rays are made. Pneumoperitoneum is found when the bowel perforation is present. Before the presentation of the acute abdomen, the patient with abdominal pain can be investigated by colonoscopy. If endometriotic nodules are transmural, these can be seen protruding through the intestinal mucosa with or without signs of (sub)mucosal bleeding (Fig. 4.8). It is difficult to make a diagnosis of rectal perforation when a patient presents with progressive nonspecific low abdominal pain. Sometimes laparoscopy is diagnostic [212].

4.4.1.7 Treatment

The appropriate management of these patients may be challenging, and a good outcome is absolutely dependent on a multidisciplinary approach. The best approach is to resect, en bloc, endometriosis and perforated bowel. If the perforation is in the small bowel, resection (Fig. 4.9) with anastomosis is performed or ileostomy if prolonged peritonitis is present. If the sigmoid colon perforates, then the Hartmann's operation is the procedure of choice [212].

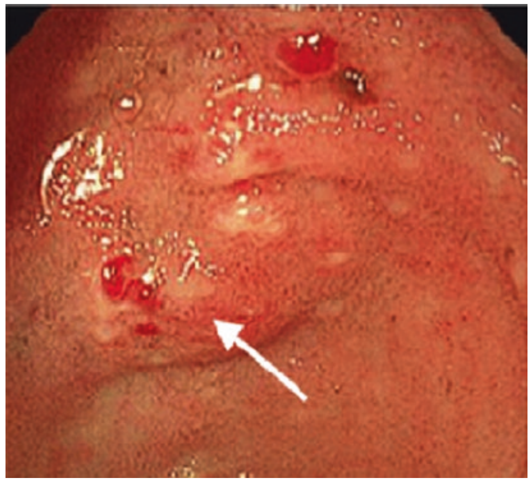

Fig. 4.8 Endoscopic image of the sigmoid colon with endometriotic infiltration of the bowel wall. Protruding spot with a small erosion (*white arrow*). Reproduced with permission from [217]

Fig. 4.9 Resected terminal ileum with infiltrating endometriosis and greater omentum. Reproduced with permission from [213]

4.4.2 Colorectal Carcinoma

Due to the extreme rarity of perforated colorectal carcinomas (CRC) in pregnancy, an overview of CRC in general during pregnancy is presented. Few cases of perforated CRC are additionally discussed.

4.4.2.1 Historical Perspective

Many reports of rectal and CRC occurring in pregnancy appear in the literature, the first being in 1835, and Cruveilhier (Fig. 4.10) reported the first case of rectal carcinoma in pregnancy in 1842. These early reports were concerned mainly with the obstetric problems of delivering the fetus in the presence of a pelvic tumor. Robert Greenhalgh (St. Bartholomew's Hospital, consulting physician to the Samaritan Hospital for Women and City of London Lying-In Hospital) in 1866 described a CS done under an ether spray on a woman with obstructed labor from a rectal carcinoma [227]. Interest in this subject lies in two effects, that of the pregnancy on the CRC and that of the complications of the CRC on the management of the pregnancy. Warren in 1957 came to the conclusion that pregnancy does not adversely affect the course of carcinoma of the rectum [228].

4.4.2.2 Incidence

The incidence of colorectal cancer in pregnancy in 1981 was 0.002% due to the fact that incidence rises with age [229]. Up to 1949, there were 75 cases published [230, 231]. Approximately 275 cases of CRC associated with pregnancy have been reported in the literature up to 1998 [232]. A review of 205 of these cases performed by Bernstein et al. demonstrated that 85% of these cancers were located below the peritoneal reflection and the mean age of 31 years (range 16–48) in a review of 42 pregnant patients with CRC [233]. First two published cases of perforated low rectal and sigmoid cancer were by Nash in 1967 [234]. The first patient was aged 38, in her fifth pregnancy (38 weeks). Artificial rupture of the membranes was carried out, and an hour later an 8 lb live boy was born. The second patient was aged 28; in her second pregnancy, in 32nd week, she had exteriorization of the sigmoid tumor. Most cases of CRC are discovered in late pregnancy, and 60–80% of the patients have rectal carcinoma [235].

Fig. 4.10 Jean Cruveilhier (1791–1874), Centenaire de la Faculté de Médecine de Paris. Portrait from 1837 (from Wikipedia)

4.4.2.3 Pathogenesis

The main pathogenesis of CRC in pregnancy is still associated with lots of unanswered questions. Some factors including pregnancy hormones, the enzyme cyclooxygenase-2 (COX-2), and tumor suppressor protein p53 were mentioned to be associated with CRC. A majority of CRC cases have been found to be positive for estrogen (20–54%) [236] and progesterone receptors (10–100%) [237]. Maybe the increased levels of estrogen and progesterone during pregnancy stimulate the growth of tumor cells with such receptors; however, all reports did not support this hypothesis. Slattery et al. in a study found only one case with positive progesterone receptor among 156 pregnant cases with CRC [236]. The elevated amounts of COX-2 in CRC patients have raised the hypothesis of its association with CRC; however, there is little evidence to elucidate its carcinogenic role.

4.4.2.4 Clinical Presentation

Common presenting signs and symptoms of CRC include abdominal pain, anemia, nausea, vomiting, and rectal bleeding. Because these signs and symptoms are also frequently found in pregnancy, physicians and patients often attribute them to the usual complications of pregnancy [235]. The diagnostic challenge for clinicians is

distinguishing pregnancy symptoms from the warning signs of CRC (Table 4.7). Clinicians must be aware of these potential warning signs and symptoms in order to make the diagnosis at an early stage of the disease. Rectal bleeding is particularly an ominous sign and should never be attributed solely to pregnancy without a proper evaluation. Presentation of perforated CRC is a sudden and severe pain, with signs and symptoms of acute abdomen.

4.4.2.5 Diagnosis

Elective Presentation

Serum CEA is an important laboratory test used in the evaluation of pregnant and nonpregnant patients. CEA levels during pregnancy are usually normal but may be slightly elevated [238].

Table 4.7 Commonly confused signs, symptoms, and laboratory results between normal pregnancy and colorectal cancer

Signs, symptoms, lab	Normal pregnancy	Pregnancy with colorectal cancer
Weight loss	In general weight gain, but women can experience weight loss in first trimester	Pregnancy can obscure weight loss secondary to CRC, primarily in second and third trimesters
Rectal bleeding	Common in pregnancy secondary to high incidence of hemorrhoids	Often attributed to hemorrhoids without pursuing appropriate workup
Nausea and vomiting	Common in pregnancy, particularly during first trimester	Often attributed to pregnancy, delaying workup
Constipation	Common in pregnancy	Often attributed to pregnancy, delaying workup
Abdominal mass	Natural process in pregnancy	Potential palpable masses secondary to CRC often missed secondary to changes of pregnancy
Anemia	Physiologic finding in pregnancy	Anemia of pregnancy masks blood loss from CRC

Reproduced with permission from [235]

CEA levels obtained prior to surgery provide a baseline to monitor the response to treatment. CEA levels also have prognostic value since increased levels prior to surgery are associated with disseminated disease and increased recurrence rates [239]. However, CEA is not useful as a tool for screening due to the low sensitivity and specificity [239].

Acute Abdomen (Perforation)

Laboratory findings show elevated levels of WBC and CRP, possible microcytic anemia, and other parameters according to the duration of the perforation. The patient can present with prerenal insufficiency due to the shift of fluid in the third space. Plain abdominal X-ray shows pneumoperitoneum if the perforation is above the peritoneal fold.

4.4.2.6 Treatment

Gestational Age: Elective Presentation

Gestational age and CRC stage are important to select treatment modality. If the tumor is resectable, standard oncological is recommended especially in those diagnosed in early pregnancy (before 20 weeks of gestation). In cases of more advanced pregnancy, surgery can be postponed at the earlier possible date at which fetus can be viable (around 32 weeks). In advanced stages, when adjuvant therapy is needed, elective abortion would help to save the mother's life, while in greater gestational ages, it is possible to pursue adjuvant therapy after early delivery. It is important that the mother be fully informed of possible risks of each choice prior to her decision. In religious countries like Iran, there is another extra challenge for parents and clinician, since due to religious beliefs, the legal abortion is only permitted up to the week 16, and after this time there would be problems to perform the abortion legally.

One-Stage or Two-Stage Procedure: Elective Presentation

If the operation is indicated in early pregnancy, then tumor resection and termination of pregnancy should be performed. It can be done in a

single act or as a two-stage procedure [240]. In the first stage, termination of pregnancy is performed. After 2–3 weeks, when the uterus returns to a normal size and the pelvic venous congestion related to pregnancy decreases, oncologic resection of the CRC is performed.

Ovarian Transposition

The primary benefit of ovarian transposition is prevention or delay of premature menopause, not the preservation of fertility. In fact, with “curative” doses in the range of 8500 cGy with external beam plus intracavitary brachytherapy, the resultant endometrial damage essentially precludes successful pregnancy, either spontaneously or with in vitro technique. Doses of radiation delivered to the ovary following successful laparoscopic oophoropexy have been determined and reported by several authors. Covens et al. [241] studied three patients in whom ovarian transposition was performed and determined the radiation dose expected to be received by the ovaries after delivery by either an external beam radiation dose of 4500 cGy or via brachytherapy. The mean dose of radiation received by the transposed ovary was 175 cGy (range, 40–370 cGy) after a mean follow-up of 2 years. The iatrogenic menopause rate was 10% overall, but iatrogenic menopause did not occur in any of the patients younger than 40 years of age.

Numerous studies have attempted to specify *radiation therapy tolerance doses* for the various tissues and structures of the body. Common dose definitions that are used to describe various tissue tolerances are the minimal tolerance dose, TD 5/5, and the maximal tolerance dose, TD 50/5, which refer to a severe complication rate of 5% and 50%, respectively, with 5 years of radiation completion. For the ovary, these values are approximately 300 and 1200 cGy, with sterility being the endpoint of severe complication. Tolerance doses for other tissues are significantly higher. In clinical practice, however, the tolerance doses for the ovary and other tissues may actually be lower, given the now common treatment regimens that typically include chemotherapy or altered radiation fractionation schemes. In general, if the ovaries can be appropriately shielded from the direct radiation beam via an oophoropexy maneuver, a dose below the TD 50/5 (300 cGy) can be achieved with a reasonable expectation of ovarian function preservation post-treatment. Simply the rule of thumb for radiation and ovarian function could be applied, meaning 10 cm distance to radiation field = 10% dose of radiation [242].

The typical outcome measure in ovarian transposition following radiation therapy is an ovarian function. This is often measured by quantitative analysis of ovary-stimulating or ovary-producing hormones as well as fertility outcomes. Spontaneous pregnancies are possible if the tubal function is preserved as part of the oophoropexy. Morice et al. [243] reported on 37 consecutive cases of ovarian transposition. In these cases, 43% of pregnancies occurred spontaneously; of these, 75% did not have the ovaries repositioned from the adnexa. Quantitative analysis of ovarian function has been reported by Covens et al. [241] in three patients undergoing ovarian transposition. Serum FSH was normal in 67% (2/3) of patients menstruating regularly 24–32 months after radiation. Treissman et al. [244] reported on a patient in whom laparoscopic ovarian transposition was performed before definitive treatment for an anal carcinoma. Tulandi and Al-Took [245] reported that normal menstruation returned after irradiation in a 34-year-old woman who underwent laparoscopic ovarian transposition before radiation for treatment of rectal carcinoma. Although post-menopausal symptoms and elevation of serum gonadotropins initially indicated ovarian failure, normal menstruation resumed and correlated with normal FSH levels 8 months after treatment. The timing depends on the treatment algorithm of rectal cancer. If the operation is indicated, it can be performed during the operation for rectal cancer. If neoadjuvant chemoradiotherapy is indicated, then laparoscopic transposition can be performed prior to neoadjuvant chemoradiotherapy.

Preservation of ovarian function by laparoscopic transposition of the ovaries before pelvic irradiation has been demonstrated to be a safe and effective procedure for patients with Hodgkin’s disease as well as in the treatment of a variety of gynecologic malignancies. Historically,

surgical exploration of the abdomen or pelvis as part of staging or resection procedures has allowed for access to the ovaries for direct-open transposition of the ovaries for planned subsequent radiation therapy.

Techniques for ovarian transposition using a laparoscopic approach vary according to the radiation field shape, size, and location. The rule of thumb for radiation and ovarian function means 10 cm distance to radiation field = 10% dose of radiation.

Medial Ovarian Transposition

Two options include (1) medial transposition of the ovaries behind the uterus (to lie beneath an external midline block) and (2) a superior transposition to the level of the iliac crest [246]. They contend that the disadvantage of the midline oophoropexy is a higher level of internal radiation scatter, as the area is generally surrounded by in-field radiation.

Lateral Ovarian Transposition

Lateral transposition includes ovarian transposition to the paracolic gutters, before radiation for gynecologic malignancies [243]. This procedure is a safe and effective method of preserving ovarian function. The peritoneum of both pelvic sidewalls is incised, and the retroperitoneal spaces developed. The common, external, and internal iliac vessels are identified. The ovarian vessels and ureters are traced on both sides. Under the direct vision of the ureters, the utero-ovarian ligaments are separated with an endoscopic linear cutting stapler. The peritoneum under and lateral to the ovarian vessels is incised to an area outside of the true pelvis, under direct vision of the ureters. At this point, the ovarian vessels could be turned laterally with a sufficient angle to maintain appropriate blood supply. The ovaries and tubes are fixed high in the paracolic gutters, below the spleen and the liver, with 2-0 silk sutures, in three points, to prevent torsion. The upper and lower poles of the ovaries are marked with hemoclips. At the end of the procedure, good blood supply to both ovaries is confirmed by a small incision of the Fallopian tubes, which are cauterized. The metal clips around the ovaries help to verify that they would be out of the radiation portals on radiation verification films [242].

Perforation

The first two published cases of perforated low rectal and sigmoid cancer were by Nash in 1967 [234]. After describing the first two patients, Nash defined two possible plans of action: if the pregnancy is sufficiently advanced, labor can be induced, the uterus emptied, and the colonic condition treated in the much easier operating conditions thus afforded; if, however, the patient's condition is too poor or if she is not yet at full term, operation must be done in the presence of the gravid uterus. In these circumstances resection is very difficult, and exteriorization is the only possible treatment. CS via an infected peritoneal cavity seems very unwise and would appear to be indicated only if a perforated rectal carcinoma obstructs vaginal delivery.

4.4.2.7 Prognosis

Maternal Outcome

The delay leads to a late diagnosis of the disease and subsequently poor prognosis. A majority of CRC cases in pregnancy present in Dukes C stage (44%) in which adjutant therapies are needed to improve the surgical outcome [233]. The median survival in a review of 42 pregnant patients with CRC was less than 5 months, and 56% died by the time of the report [247].

Fetal Outcome

CRC in pregnancy represents a serious threat to both the mother and the fetus. Data confirm that 78% of pregnancies in women with colonic tumors above the rectum resulted in healthy, liveborn infants. Prematurity, intrauterine death, stillbirth, and termination were all contributors to the death of these infants [248].

Genetic Counseling

CRC occurs rarely in young patients, and as a result, this patient population is more likely to have strong predisposing factors compared to the general population of patients with CRC [249]. Such predisposing factors for CRC include hereditary nonpolyposis CRC (Lynch syndrome), familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, and long-standing inflammatory bowel disease. However, these

increased risk groups represent only a small portion of CRC diagnosed in pregnancy [232]. A review of 19 pregnant patients by Girard et al. from 1981 demonstrated that 21% of patients had one of these strong predisposing factors for CRC [229]. Despite the negative result for possible hereditary nonpolyposis colon cancer (*Amsterdam II criteria*), *Bethesda criteria* should be checked for microsatellite instability. If the microsatellite instability testing is positive, the genetic testing of the three genes associated with HNPCC should proceed. Once a mutation was identified in the family, other family members could consider predictive testing.

4.4.3 Spontaneous Colorectal Perforation

There are two causes of spontaneous perforation of the colon: stercoral and idiopathic.

4.4.3.1 Stercoral Perforation

Incidence and Diagnostic Criteria

Stercoral perforation is rare, even in nonpregnant patients. The first case of (possible) stercoral perforation was described in 1894 by Pavy [250]. The review identified only 88 cases from 1894 to 2000, and authors proposed diagnostic criteria for stercoral perforation [251]:

- Round or ovoid perforation, ≥1 cm in diameter, antimesenteric location
- Fecaloma (hard, laminated, inspissated fecal mass) within the colon, protruding through the perforation site or lying within the peritoneal cavity
- Typical pathohistological features (pressure necrosis or ulcer with chronic inflammatory reaction around the perforation site)
- The absence of other active colonic pathology, such as diverticulitis, carcinoma, and Hirschsprung's disease

Stercoral perforation during pregnancy is extremely rare, with only three cases published: women presented at 22, 36, and 41 weeks of pregnancy [252–254].

Risk Factors

Chronic constipation is the main risk factor, present in 81% of patients. Use of antacids, codeine-containing narcotics, nonsteroidal anti-inflammatory agents, major tranquilizers, and tricyclic antidepressants has been linked to stercoral perforation [255, 256]. These medications are all known to cause constipation.

Treatment

Treatment is surgical, and resection of the diseased segment with proximal colostomy and closure of the rectal stump or mucous fistula are the procedures with the lowest mortality rate in general population [255]. This is the recommended procedure in pregnant population and was performed in two pregnant cases [253, 254].

Prognosis

The reported mortality rate among all cases in a general population of stercoral perforation is 47%, with a 35% mortality rate among surgically treated cases [255]. Of three pregnant patients [252–254], one died (maternal mortality of 33%). Perinatal mortality is 66% probably due to prolonged peritonitis. The first patient presented at 41 weeks of gestation delivered a stillborn infant and died after delivery. Stercoral perforation was diagnosed on autopsy [252]. The second patient in 36 weeks of pregnancy was explored and CS performed, with a live baby, before the Hartmann's procedure [253]. The third had a sigmoid perforation at 22 weeks of pregnancy. One day after the Hartmann's procedure, the patient delivered vaginally a dead female infant [254].

4.4.3.2 Idiopathic Perforation

The features of idiopathic perforation of the colon are [257]:

- Linear perforation
- No feculent ulcer at the microscopic examination

- Clear mucosal edge not extending to the serosa
- Regularly broken ends of the muscular layer

There is no published case of idiopathic colorectal perforation.

4.4.3.3 Spontaneous Intestinal Perforation

Incidence

This is an extremely rare entity, and the incidence is unknown. In 1959 seven cases were reported of nontraumatic/nonendometriotic intestinal rupture during pregnancy with 85% mortality [192].

Risk Factors

All risk factors for "spontaneous" ischemic events in general population are also risk factors in pregnancy (Table 4.8). The difference is in the incidence of different risk factors due to the specific age of presentation. Also, pregnancy per se is a risk factor for thromboembolic events. The combination of different risk factors could be present and should be kept in mind which aggravates the possibility of intestinal ischemia and subsequent perforation. Most spontaneous intestinal perforations are due to previously unknown but present risk factors. There are cases when women during early pregnancy (by mistake because unaware of pregnancy) [258] or early postpartum period by patient itself [259] take oral contraceptives with the development of mesenteric vein thrombosis. These risk factors are the same and could include the perforation both on the small and large bowel.

Table 4.8 Possible risk and combinations of factors for *spontaneous* intestinal perforation [257, 260, 261]

Antiphospholipid syndrome (macroangiopathy)
HELLP syndrome (microangiopathy)
Syphilis
Vasculitis
Low-flow states
Arrhythmia
Sepsis
Shock
Disseminated intravascular coagulation
Recent surgery/C-section
Thromboembolism
Ischemia caused by previous surgical manipulation
Cocaine abuse
Valvular heart disease
Infective endocarditis
Diabetes mellitus
End-stage renal disease
Idiopathic hypertension
Oral contraceptives

Prevention

Obstetric complications are the other hallmark of antiphospholipid syndrome. It is recommended that all women with antiphospholipid syndrome should maintain antithrombotic treatment throughout their entire pregnancy and during the postpartum period. The prevention of choice is combined low-dose aspirin and full antithrombotic doses of low-molecular-weight heparin. In high-risk groups, such as the history of previous thrombotic events, warfarin may be used during pregnancy, but only after organogenesis (6th–12th weeks) because of high risks of fetal malformations.

Treatment

The type of the operation depends on the extent of peritonitis and underlying ischemia. If the perforation is present without visible ischemia, resection with anastomosis is the preferred method. If there are signs of ischemia, the ischemic segment is resected and anastomosis with or without stoma is performed. In long-standing generalized peritonitis, the stoma is the preferred option.

4.4.4 Instrumental Abortion

4.4.4.1 Incidence

Bowel perforation secondary to illegally induced abortion though rare and uncommon in the developed world is a significant and major cause of maternal morbidity and mortality in developing or especially undeveloped countries where abortion laws are still restrictive and most abortions are performed clandestinely and illegally by unqualified personnel [262, 263]. The increased

incidence of abortion-related complications such as bowel injuries has been reported in most developing countries [264]. Ignorance and inability to take a quick decision regarding termination of an unwanted pregnancy compel a large number of women to seek illegally induced abortion in the second trimester from an unauthorized person in unrecognized places. The rate of bowel perforation as a complication of induced abortion has been reported to the range 2–18% of all abortion-related complications [265–269]. However, many cases may have been unreported because of its medicolegal implications [270].

4.4.4.2 Treatment

Surgical intervention is considered to be the gold standard treatment for patients with bowel injury/perforation following instrumental abortion [270]. All patients underwent surgical treatment [265, 266, 270–275]. One of the many factors affecting the surgical outcome in patients with bowel perforation is time interval from perforation to laparotomy [270]. Early surgery can minimize the complications, while delayed surgery leads to severe peritonitis and septic shock. The majority of patients in developing countries were operated more than 24 h after the onset of illness [265, 270]. Delayed definitive surgery may be attributed to late presentation due to lack of accessibility to health-care facilities and lack of awareness of the disease; as a result, some patients with bowel perforation following induced abortion may decide to take medications in the prehospital period with the hope that the symptoms will abate. It is also possible that some clinicians managing the patients initially may not have considered perforation as a possible diagnosis leading to delayed referral to tertiary care hospital. The ileum and the rectosigmoid colon are the most common parts of the bowel affected [265, 266, 270–275]. The relative fixity of these portions of the bowel has been suggested as a possible reason. Early surgical interference is the optimal treatment option for perforation. However, the type of surgery to be applied is controversial [270].

The surgical management of small intestinal injuries is fairly straightforward with minimal sequel. The practice in managing these patients is a simple closure in solitary perforations and segmental intestinal resection and primary anastomosis in multiple perforations or gangrenous bowel. The management of large bowel injury is more controversial [270, 272]. This is more so when the left colon is involved. A simple colostomy has been reported to be the safest approach in the management of these injuries. Other options include primary repair, resection and primary anastomosis, and repair with a proximal protective colostomy or ileostomy. A simple colostomy is easier and faster to accomplish in these poor surgical risk patients. However, the major drawback of colostomy is the need for a second operation to restore intestinal continuity, the specialized care before closure, and the attendant cost which reduces its popularity [265, 266, 270–275]. The challenge is even more conspicuous in a developing country like Tanzania where resources for caring of patients with colostomy are limited. The management of stoma remains difficult in developing countries because of the shortage of suitable equipment in this respect, and peristomal ulceration remains a major problem [265, 266, 270–275]. Primary repair and resection and primary anastomosis are rarely performed, only in case of viable bowel, whereas colostomy is reserved after resection of a gangrenous large bowel.

4.4.4.3 Prognosis

The recent overall complication rate in developing countries is around 50% [265, 272]. The difference in complication rates can be explained by differences in antibiotic coverage, meticulous preoperative care and proper resuscitation of the patients before operation, improved anesthesia, and somewhat better hospital environment. Surgical site infection was the most common postoperative complication [272, 273]. The high rate of surgical site infection may be attributed to contamination of the laparotomy wound during the surgical procedure. Maternal mortality ranges 8–27% [265, 272, 273]. The high mortality rate is attributed to high gestational age at termination of pregnancy, late presentation, delayed surgical treatment, and postoperative complications.

The median length of hospital stay is variable, from 12 days [272] to significantly longer hospitalizations [273]. Self-discharge against medical

advice is a recognized problem and this is rampant, especially among patients with complications of illegally induced abortions. Similarly, poor follow-up visits after discharge from hospitals remain a cause for concern. These issues are often the results of poverty, long distance from the hospitals, and ignorance.

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5 Symptomatic Abdominal Wall Hernia

Abstract

A hernia is an area of weakness or complete disruption of the fibromuscular tissues of the body wall. Abdominal wall hernias are not common during pregnancy because these are commonly repaired before a planned pregnancy to avoid possible complications during gestation. Hernias can be symptomless or have minimal symptoms, including slight discomfort or pain. Such hernias are not life-threatening and should be controlled on regular basis during pregnancy. Conservative measures should include weight control, the avoidance of heavy lifting, stool softeners, and abdominal binders. After spontaneous delivery and uterine involution, hernias should be repaired on an elective basis. It is of utmost importance for a clinician to diagnose emergent situations, which include incarceration, strangulation, and bowel perforation caused by a hernia because consultation with a surgeon and emergency operation are mandatory. There is still no consensus for an irreducible hernia during pregnancy, but complications during pregnancy outweigh semi-elective operation. (Incarcerated) gravid uterus in a hernia poses a specific problem because there is a higher risk of fetal death or obstetric complications. In this situation, operative treatment is almost a rule, which includes simultaneous obstetric and surgical management.

Surgical repair of different types of a hernia is the most common general surgical procedure. More than 20 million patients worldwide undergo hernia repair each year [1]. As the world population grows, there is a continuous increase in an absolute number of hernias which should be repaired. Also as the world population grows, it is obvious that there are more and more pregnant women throughout the world. Therefore, there will be more pregnant women with hernias presenting in elective or emergent settings. Minimization of this increase would probably be due to more widespread use of laparoscopy which in turn lowers the incidence of postoperative hernias.

Pathophysiology of development and progress of abdominal wall hernias in pregnancy is caused by hormonal changes and increased intra-abdominal pressure during enlargement of the gravid uterus. Pathophysiology of increased intra-abdominal pressure during pregnancy is presented in detail in Chap. 22.

5.1 Groin Hernia

Varices of the round ligament are often mistaken for an inguinal hernia

Verovitz CH, 1941

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_5

5.1.1 Incidence

5.1.1.1 General Population

Estimated rates of the lifetime risk of inguinal hernia repair are 27% for men and 3% for women in general population [2]. Operations performed for both elective and emergent inguinal hernias in women have a bimodal age distribution: during the first 9 years of life; thereafter, incidence rises after 30 years of age. The incidence in women is nine to ten times less frequent than in men, and only 9% of inguinal hernioplasties are performed on women; of these, 17% are performed on an emergent basis [2]. In nonpregnant women, the indirect inguinal hernia is 2.5 times more frequent than a direct hernia during elective operations (54.3% vs. 23.1%), while the difference during emergent operations is significantly smaller (23.5% vs. 17.2%). Femoral hernias in an elective setting comprise 15.9%, while as an emergency these comprise 53.6% [3].

5.1.1.2 Pregnancy

An inguinal hernia in pregnancy has a reported incidence of 1/1000–1/3000 with 75% occurring in multiparas [4, 5]. The incidence of incarcerated/strangulated groin hernias in pregnancy is unknown but is at least ten times lower due to several factors. First patients with a hernia planning pregnancy undergo an operation before or after pregnancy, therefore, lowering the incidence in future pregnancies. Growing uterus blocks the entrance of intra-abdominal contents in the hernia sack. Also before the era of ultrasound, probably a significant portion of patients' intraoperative findings did not reveal a hernia but other pathologies in this region (see Sect. 5.1.4) [6].

5.1.2 Etiopathogenesis and Risk Factors

Some authorities from the previous century stated that preexisting hernia frequently disappears during the later months of pregnancy: *the reason being that the enlarging uterus pushes the intestines away from the inguinal ring and presently blocks access to them* [7]. Strangulated inguinal hernias are extremely rare in the later months, and, in fact, Gaudier in 1894 stated that a strangulated inguinal hernia and pregnancy are incompatible [8]. That is probably incorrect, at least partly, because many groin lumps first appearing in pregnancy are due to varicosities of the round ligament, which at first sight simulate an inguinal hernia. Praxagoras of the third to fourth century BC was credited with the first reported operation for obstruction in general population, by relieving strangulated inguinal hernia [9]. The risk factors (Table 5.1) are the same as for the general population plus the increase of intra-abdominal pressure due to an enlarging gravid uterus.

Table 5.1 Risk factors during pregnancy for abdominal wall hernia

Family history
Collagen diseases
Smoking
Renal failure
Chronic lung disease
Diabetes mellitus
Steroid use
Malignancy
Malnutrition
Cirrhosis
Ascites
Obesity

5.1.3 Clinical Presentation

Diagnosis is made by the presence of a reducible or nonreducible groin lump, which demonstrates an expansile cough impulse and the exclusion of other causes of a lump. Palpation of hernia content can differentiate a solid structure (greater omentum or uterine fibroid) from the intestine (gas sounds on pressure). Assessment of the inguinal region is made by applying Valsalva maneuver which increases intra-abdominal pressure. The maneuver is performed when a person tries to exhale forcibly with a closed glottis so that no air exits through the mouth or nose as, for example, strenuous coughing, straining during a bowel movement, or lifting a heavy weight. If incarceration occurs, there is a severe abdominal pain with nausea and sometimes vomiting. If the bowel is incarcerated, then severe vomiting sometimes with the absence of stool and flatus is

present. Fever develops if perforation due to distention or strangulation occurs. In such cases, redness of the overlying skin can be found due to spread of infection through the abdominal wall.

5.1.4 Differential Diagnosis

There are many causes of a groin swelling/mass and some are listed in Table 5.2. The causes of groin swelling specific to pregnancy are discussed in detail.

5.1.4.1 Round Ligament Varicosities

Incidence

Round ligament varicosities (RLVs) are rare, and their true incidence is unknown [12, 15, 16] probably because RLVs are underdiagnosed. It is probably due to the general opinion that pregnant patients should have some degree of pain during pregnancy. McKenna et al. claim the incidence of 0.001% [10]. The RLV was first reported in 1941 by Verovitz who stated that "varices of the round ligament are often mistaken for an inguinal hernia" [17]. The first report of RLV during pregnancy in Korea was in 2010 by Jung et al. [18].

Pathophysiology

Anatomically, the round ligament extends from the lateral uterus to the major labia containing veins, arteries, lymphatics, and nerves. RLVs are prominent veins within the round ligament and are more common in pregnancy especially in the second or early third trimester because pregnancy promotes increased venous flow and reduced venous tone [14]. There are several mechanisms that cause RLV development. Physiologically, there are progesterone receptors naturally occurring within the round ligament veins [15], and, as progesterone levels increase during pregnancy, progesterone-mediated venous smooth muscle relaxation causes dilation of these veins. Furthermore, with advancing pregnancy, blood volume and cardiac output increase resulting in an increase of venous return, especially during exercise [19]. This, as well as a gravid uterus, causes relative impingement of pelvic veins, resulting in venous engorgement.

Table 5.2 Causes of groin swelling/mass [10–14]

Lymphadenopathy
Subcutaneous lipoma
Cyst in persistent processus vaginalis
Round ligament varicosities
Round ligament stretch
Inguinal endometriosis
Inguinal metastases
Lymphoma
Hematoma
Abscess
Mesothelial cysts
Cyst of the canal of Nuck
Aneurysms/pseudoaneurysms
Soft tissue malignancies
Cystic lymphangiomas

Clinical Presentation

The distinction between a groin hernia and RLV is difficult clinically because the symptoms and signs are similar. Both swellings disappear on lying down and reappear on standing, provoked by increased intra-abdominal pressure in cases of coughing or Valsalva maneuver, though a varicocele may return more gradually than a hernia and is a little less circumscribed. Reducibility of RLV is due to the fact that these veins do not contain valves and therefore can partially empty. RLVs also transmit cough impulses because transmitted abdominal pressure leads to vein distention [13, 14], a clue that may suggest RLV is in the coexistence of lower limb or labial varicosities. An RLV is dull on percussion and more closely resembles a hernia containing omentum than one containing the bowel. The absence of varicose veins elsewhere does not exclude the diagnosis of an RLV. Both traverse the inguinal canal and can be reducible or irreducible. RLV most commonly presents with a groin bulge and mild discomfort (Fig. 5.1).

Round ligament varicose vein thrombosis. If the pain is the predominant symptom, thrombosis of RLV or variceal rupture should be excluded [21]. Thrombosis of the RLV is a complication which still further increases the resemblance between an inguinal hernia and RLV. Thrombosis produces a firm, tender, irreducible swelling simulating a strangulated inguinal hernia. It is more common during the postpartum period (Fig. 5.2).

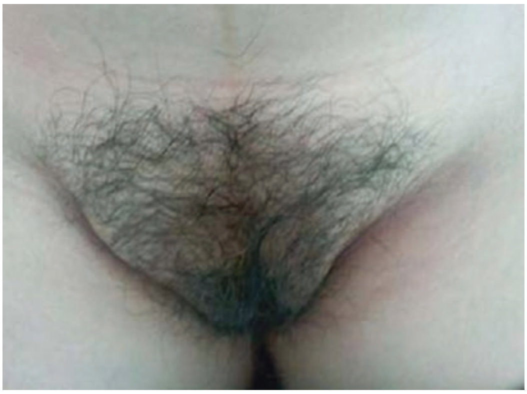

Fig. 5.1 Right inguinal swelling caused by round ligament varicosities. Note the *linea nigra* of pregnancy. Reproduced with permission from [20]

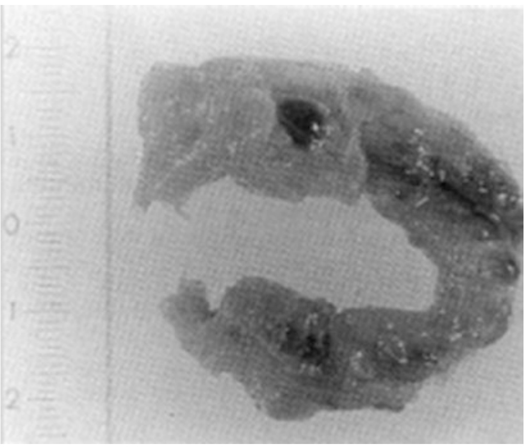

Fig. 5.2 The excised part of the round ligament which is thickened with evident thrombosed varicose veins. Reproduced with permission from [21]

Diagnosis

Ultrasonography of the inguinal region can differentiate between multilocular mass (multiple echo-free serpentine tubular channels) which enlarges during Valsalva maneuver (Fig. 5.3) and single mass found in a hernia which also enlarges during Valsalva maneuver. If the bowel is present in the sac, then peristalsis can be visualized and helps to differentiate it from RLV. Color Doppler US examination can differentiate RLV from other causes of groin swelling in pregnancy. The characteristic ultrasound appearances of varicosities simulating pelvic masses in pregnant and nonpregnant women include a prominent venous plexus with accompanying dilated draining veins passing through the inguinal canal, veins draining into the inferior epigastric vein, and the typical *bag of worms* appearances of smaller varices [22] with the absence of bowel or lymph nodes in the inguinal mass [10]. Duplex imaging can confirm venous flow and augmentation of this flow with Valsalva maneuver (Fig. 5.4). In inguinal hernias, herniated bowel may be recognized by its peristalsis, mucosal blood flow, or mesenteric fat by US and Doppler US examination [16]. Lymph nodes have a characteristic appearance, usually hypoechoic with an echogenic central hilum that demonstrates flow on Doppler imaging. The sonographic appearance of endometriosis, hematoma, lipoma, or lymphadenopathy is not easily confused with that of RLV [16]. In doubtful cases, CT or MRI can be used.

Round ligament varicose vein thrombosis. The diagnosis of thrombosis of RLV has relied historically on surgical evaluation [23], but at imaging, they should be suspected if veins are noncompressible, no flow signal can be obtained, and/or there is a visible clot within the lumen.

Treatment

There is no specific treatment and most symptoms resolve completely from 2 weeks [20] to 2 months postpartum [10]. After delivery, when pelvic venous obstruction by the gravid uterus is relieved, the spontaneous resolution will occur in most patients. A truss may, by giving support, add to the comfort of the patient. Reassurance, with a simple explanation of the temporary nature of the lump during pregnancy and the recommendation of the usual supportive measures for the relief of vulvar and leg varicose veins, is all that is necessary.

Round ligament varicose vein thrombosis. There is no consensus on the management of thrombosed RLV, with patients being treated successfully both with conservative and with surgical management [21]. Surgical exploration is recommended first to rule out a strangulated hernia and second to reduce pain or discomfort caused by the inguinal mass.

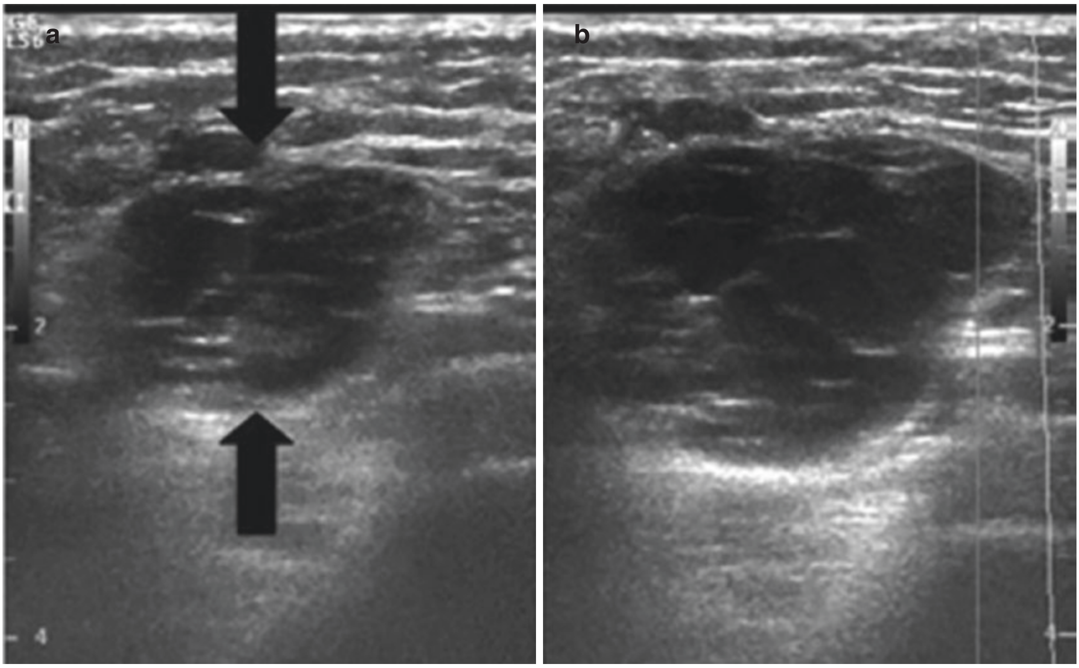

Fig. 5.3 (**a**) Transverse gray-scale sonogram of painful right reducible inguinal mass at rest shows cystic mass (*arrows*). (**b**) Mass enlarged during Valsalva maneuver. Reproduced with permission from [9]

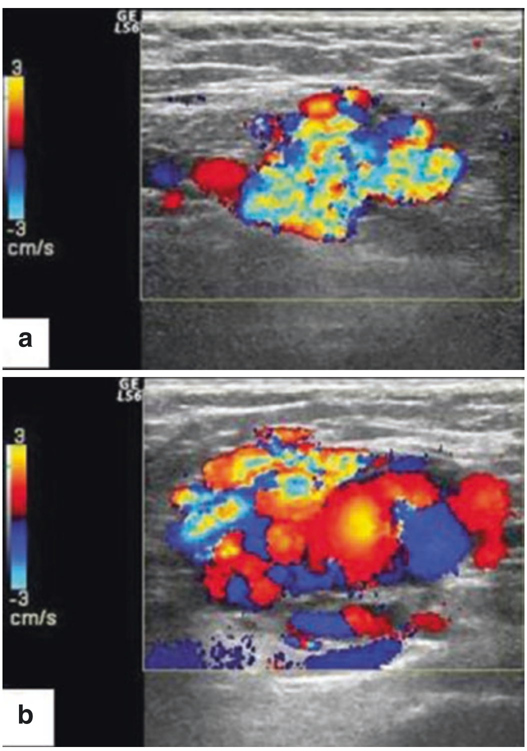

Fig. 5.4 (**a**) Color Doppler US examination confirmed venous flow in the mass. (**b**) Valsalva maneuver caused marked enlargement and flow augmentation in the veins, consistent with round ligament varices. Reproduced with permission from [9]

5.1.4.2 Round Ligament Stretch/Pain

As the uterus rises in the abdomen, it pulls on the round ligaments and stretches them (Fig. 5.5). The ligaments usually stretch easily, but occasionally growth rate is too much for them and small hematomas occur. The patient will have sudden localized abdominal pain around hip area that is either on one side or both with the little constitutional upset. Some women even report pain that extends into the groin area. Examination shows tenderness well localized over the round ligaments and sometimes radiating to their insertion along the inguinal canal and to the pubic tubercle. Treatment with analgesia, bed rest, and local warmth resolves the situation in a few days.

5.1.4.3 Inguinal Endometriosis

Endometriosis (ectopic decidua in pregnancy) is defined as uterine mucosa found outside the endometrial cavity that can respond to ovarian hormonal stimulation. Abdominal wall endometriosis is any ectopic endometrium found superficial to the peritoneum without suggesting an association with a surgical procedure. Inguinal endometriosis is rare with the incidence of 0.3% of endometriosis treated in general population.

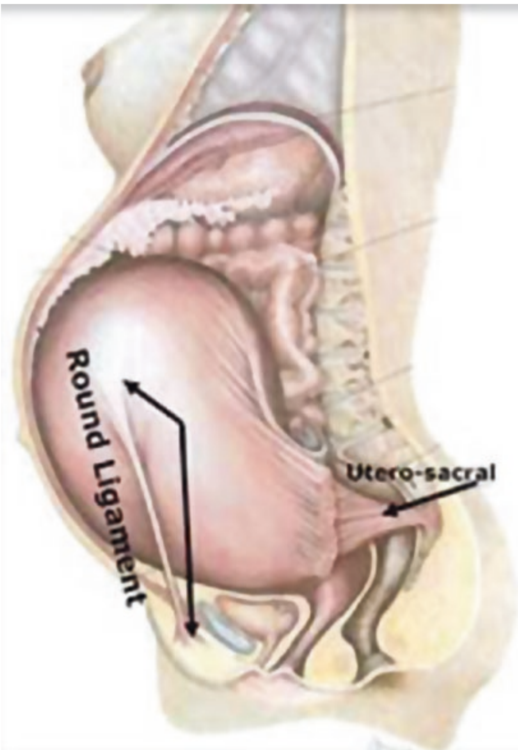

Fig. 5.5 Enlargement of the pregnant uterus causes distention of the round ligament producing abdominal pain. Reproduced with permission from [24]

The incidence of endometriosis in the extraperitoneal part of the round ligament is 0.3–0.6% among women suffering from endometriosis in general [25–28]. Almost all lesions are on the right side, and the lowest incidence is of bilateral inguinal endometriosis [25, 27]. Although predominance for the right side is unclear, one possibility for the right-sided predominance is that the sigmoid colon relatively protects the left groin [29]. Also, the right inguinal area seems more often affected because of the clockwise movement of the peritoneal fluid and the peristaltic movement of the intestinal wall [30]. The diameter of the mass ranges 1–6 cm [25, 26].

In 25% of published cases, inguinal endometriosis is associated with an inguinal hernia.

Endometriosis in the inguinal region was first reported by Cullen in 1896 which he referred to as a "adenomyoma of the round ligament" [31], and since then less than 100 cases have been published. There are several theories of its origin like (1) congenital, (2) metaplasia, (3) metastasis, (4) implantation, and (5) direct extension of endometrial tissue along the round ligament as a possible pathogenesis of inguinal endometriosis [28]. The prevalence of the round ligament of uterus endometriosis in females with deep infiltrating endometriosis is 13.8% [32]. The canal of Nuck, which is a small evagination of the parietal peritoneum that accompanies the round ligament through the inguinal ring into the inguinal canal, provides the most likely pathway for endometrial tissue to implant in the superficial inguinal soft tissue (Fig. 5.6) [33].

The symptoms commonly fluctuate with menses. Catamenial or cyclic pain is the pathognomonic symptom in the differential diagnosis of the inguinal mass. Unfortunately, only 57% of patients present with cyclic symptoms. Another common symptom is bleeding from superficial lesions. Symptomatic complaints ranged from 3 months to 10 years, with an average interval of 3 years [25, 27]. There is also a significant time delay between a patient's index surgery and the onset of symptoms in scar endometriosis. Patients develop symptoms on an average of 3.6 years. It is essential to point out that cyclicity is not always demonstrable and is not essential for diagnosis. Despite fluctuating symptomatology inguinal endometriosis should be included in a differential diagnosis because it is often diagnosed as an inguinal hernia preoperatively. Until the 1960s correct preoperative diagnosis was made in 25–35% (ultrasound of inguinal region was not described) [28].

The sonographic findings of inguinal endometriosis have been presented for fewer than 15 cases [29, 34–36]. The sonographic features of inguinal endometriosis are variable. The presence of solid masses [35], cystic masses [29, 37], and combined cystic and solid masses [36] has been described. Most of the cystic masses have internal septa (Fig. 5.7) [29, 32, 37]. These sonographic findings are different from findings for

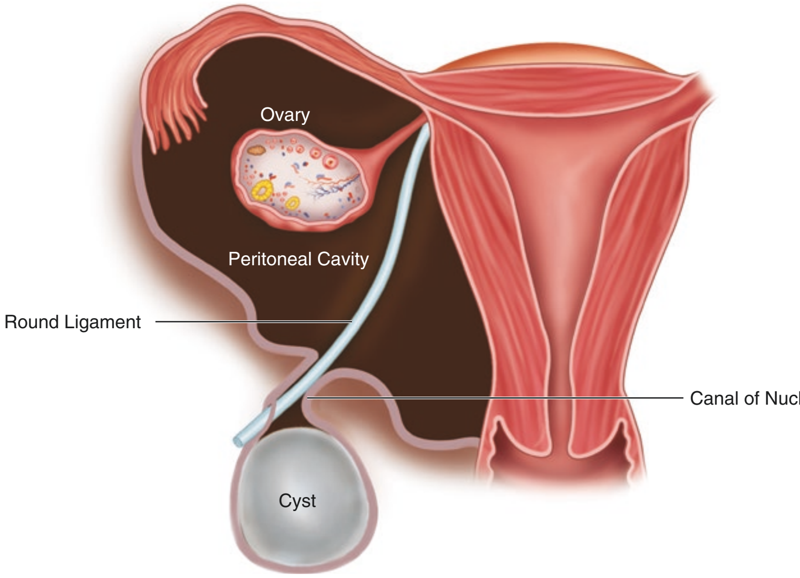

Fig. 5.6 Anatomic diagram of the canal of Nuck. The canal is a small evagination of the parietal peritoneum that accompanies the round ligament through the inguinal ring into the inguinal canal, providing the most likely pathway for endometrial tissue to implant in the superficial inguinal soft tissue. Reproduced with permission from [34]

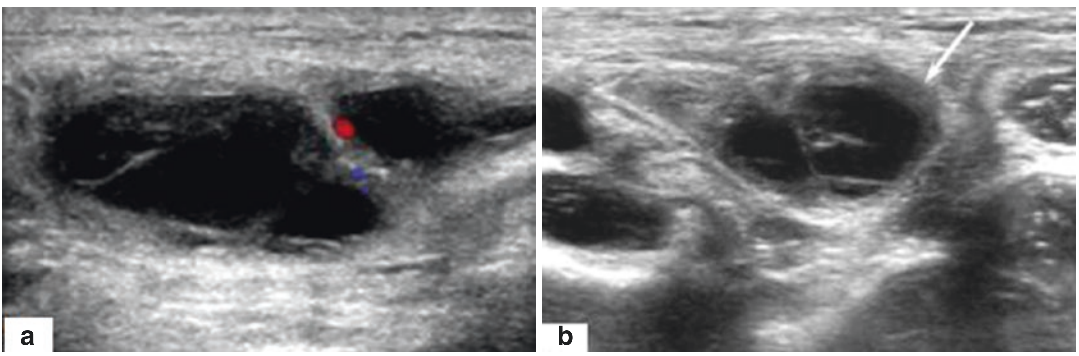

Fig. 5.7 Imaging findings for inguinal endometriosis in a 29-year-old woman. Longitudinal color Doppler (**a**) and transverse gray-scale (**b**) sonograms showing a cystic mass with an internal septum in the right inguinal area (*arrow*). There are flow signals within the septum. Reproduced with permission from [34]

abdominal wall endometriosis that arises near Cesarean section (CS) scars. Most abdominal wall endometriosis shows subcutaneous discrete nodule, hypoechoic with scattered hyperechoic strands, and irregular, often spiculated, margins infiltrating the muscularis fascia, circumscribed by a complete or incomplete hyperechoic ring caused by a perilesional inflammatory reaction (Fig. 5.8). No vascularity or only internal lesional vascularity could be present on color Doppler sonography. Lesions larger than 3 cm, small cystic areas may be detected, possibly because of small blood lacunae of recent hemorrhage. Young et al. believe that this difference is due to the different environmental situation between the two types of lesions. Inguinal endometriosis usually develops in the canal of Nuck, which is a cavity filled with fluid. If bleeding occurs within the implanted endometrial tissues, the canal of Nuck may be obliterated, and the structure may be vulnerable to the formation of a cystic mass. In contrast, cyst formation is difficult for abdominal wall endometriosis because this lesion usually occurs in CS scars, which is a limited space rather than the canal of Nuck [32]. Sonographically guided fine-needle aspiration is helpful for rapid and accurate diagnosis of inguinal endometriosis and enables a malignancy to

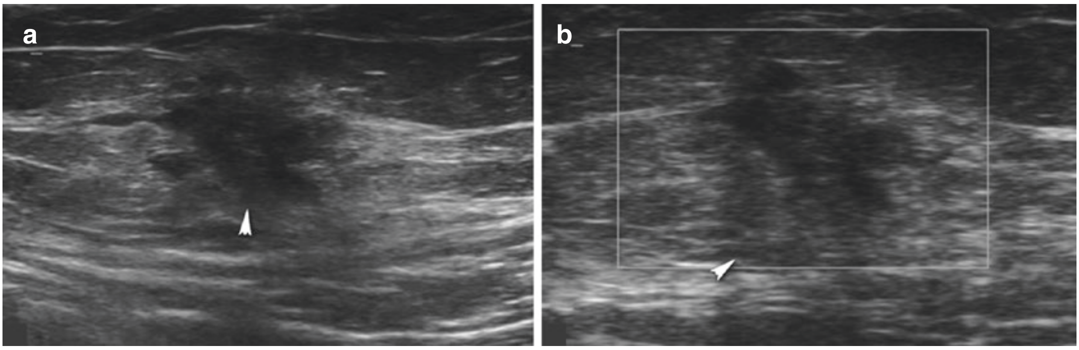

Fig. 5.8 Abdominal wall (scar) endometrioma (*arrow*). (**a**) The transverse sonogram shows irregularly shaped, hypoechoic solid mass in the subcutaneous fat. (**b**) Power Doppler sonography shows absence of vascularization. Reproduced with permission from [41]

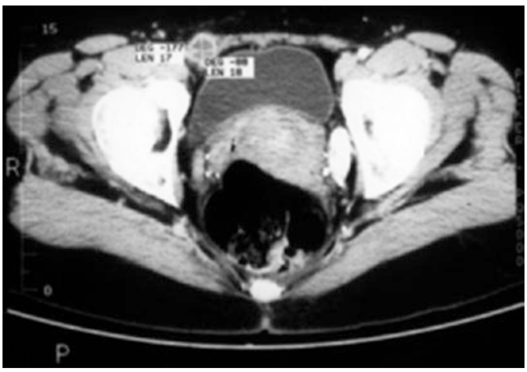

Fig. 5.9 CT scan of the right inguinal extraperitoneal endometriosis. Low-density area with an enhancing rim in the right inguinal region medial to the inferior epigastric vessel lying lateral to the inferior insertion of the rectus abdominis muscle. There was no evidence of bowel obstruction, but there were inflammatory changes around the area suggestive of a strangulated direct inguinal area. Reproduced with permission from [42]

be excluded (only when abdominal wall hernia is ruled out) [38]. On computerized tomography (CT) scan, inguinal endometriosis shows the presence of a soft tissue mass which is mainly solid in nature with the same density as muscle and follows the course of the round ligament (Fig. 5.9). An additional diagnostic modality in unequivocal cases is magnetic resonance imaging (MRI) with a characteristic *shading sign* representing an endometriotic nodule [39]. MRI clearly shows the change of tumor size depending on the menstrual cycle, adding at the correct diagnosis of endometriosis in unusual locations [40]. However, in half of the reported cases of inguinal endometriosis, MRI features were not specific and included intermediate or high signal intensity on T2-weighted images [35, 40]. When inguinal endometriosis presents as a solid mass on sonography, the differential diagnosis includes neoplasms such as sarcoma, lymphoma, metastasis, enlarged lymph node, an abscess, and hematoma. When inguinal endometriosis presents as a cystic mass on sonography, it should be differentiated from a hydrocele of the canal of Nuck (usually presents as a unilocular cyst [33] and an inguinal hernia).

A definitive diagnosis is made during operation for inguinal hernia repair, and the condition is treated by complete excision of the inguinal endometriosis, including the extraperitoneal portion of the round ligament (Figs. 5.10 and 5.11); otherwise, recurrences are frequent [43]. Intraperitoneal endometriosis is demonstrated in most patients. Many recommend pelvic laparoscopy for all patients who have endometriosis in the extraperitoneal part of the round ligament or in a scar because of the association with pelvic endometriosis and subfertility (Fig. 5.12) [25, 26]. Seydel et al. did not recommend laparoscopy in patients who do not

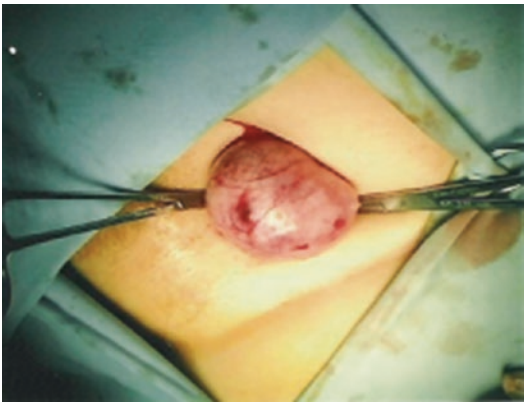

Fig. 5.10 Right inguinal mass (endometriosis) during exploration. Reproduced from [30] under the CC BY 2.0

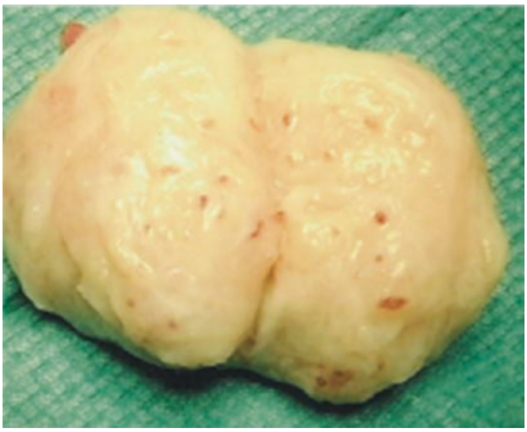

Fig. 5.11 Gross specimen of right inguinal endometriosis. Reproduced from [30] under the CC BY 2.0

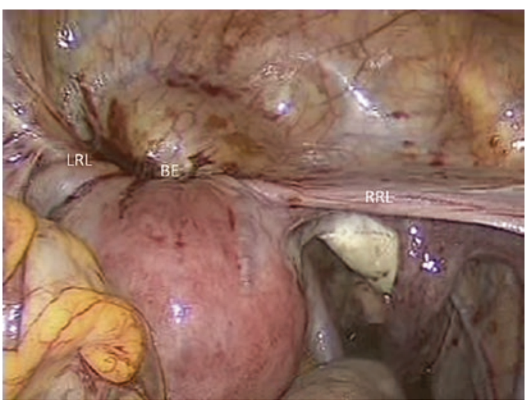

Fig. 5.12 Macroscopic aspects of the round ligament of the uterus. *LRL* a left round ligament that is shortened, widened, and deviated in the direction of the bladder due to endometriosis. *RRL* a right round ligament that is thickened and pressured by uterine deviation to the left. *BE* bladder endometriosis. Reproduced with permission from [32]

present with signs of pelvic endometriosis [44]. Only 13% of the patients with abdominal wall endometriomas had a history or subsequent diagnosis of pelvic endometriosis [45]. This percentage is within the range of the overall incidence of pelvic endometriosis in menstruating females (8–15%) [46]. Hence, these data suggest that the incidence of pelvic endometriosis in patients with abdominal wall endometriomas is within the same range as the general population.

5.1.4.4 Hydrocele of the Canal of Nuck

In the female, the round ligament is attached to the uterus near the origin of the Fallopian tube, and a small evagination of parietal peritoneum accompanies the round ligament through the inguinal ring into the inguinal canal [47]. This small evagination of parietal peritoneum is the canal of Nuck in the female, homologous to the processus vaginalis in a male. The canal of Nuck normally undergoes complete obliteration during the first year of life. Failure of complete obliteration results in either an indirect inguinal hernia or a hydrocele of the canal of Nuck [47, 48]. If obliteration fails in the distal portion of the canal, a sac containing serous fluid remains—the so-called hydrocele of the canal of Nuck [47, 48]. Hydrocele of the canal of Nuck is a rare condition. Clinically, the hydrocele of the canal of Nuck manifests as a painless swelling in the inguinal area and major labia. The cysts are usually small averaging about 3 cm in length and about 0.3–0.5 cm in diameter [49]. Ultrasound finding of a hydrocele of the canal of Nuck is typically sausage shaped, extending along the route of the round ligament [48], or comma shaped with a surface beak representing a continuation of the peritoneal cavity through the inguinal canal on ultrasound [33]. MRI shows a hydrocele of the canal of Nuck as a thin-walled tense cystic mass in inguinal area (Fig. 5.13). During operation cystic mass adjacent to round ligament is found (Fig. 5.14). It should be excised completely with excision of the adjacent round ligament because the definitive diagnosis is sometimes established only during pathohistological analysis.

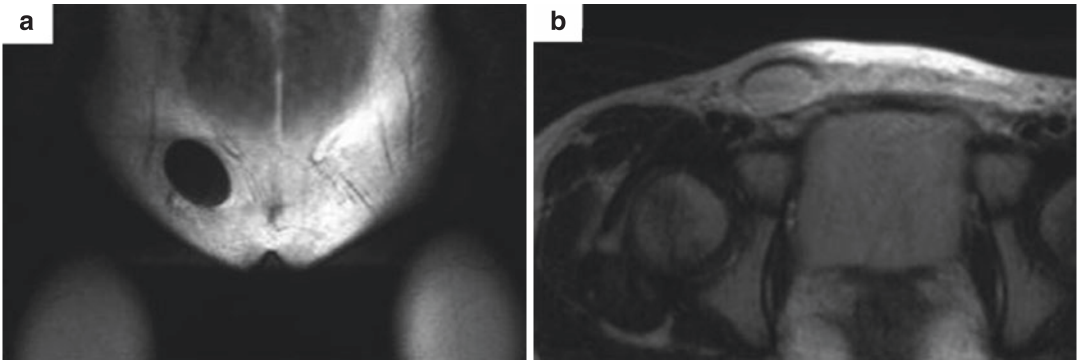

Fig. 5.13 MRI findings of a hydrocele of the canal of Nuck. (**a**) Coronal T1-weighted and (**b**) axial T2-weighted images show the mass is true cystic and thin walled in the right inguinal area. Reproduced with permission from [33]

Fig. 5.14 Photograph at surgery shows a comma-shaped cyst with surface beak continuing the round ligament that extends peritoneal cavity through the inguinal canal. The round ligament with cystic tense mass was excised. Reproduced with permission from [33]

5.1.5 Diagnosis

5.1.5.1 Plain Abdominal X-Ray

It is used for the confirmation of bowel obstruction due to incarcerated inguinal hernia in general population. If a bowel obstruction is not present, probably the part of the greater omentum is incarcerated. This imaging method is not mandatory because clinical suspicion of incarcerated inguinal hernia is an indication for the emergency operation during pregnancy or transabdominal ultrasound if clinically other diagnoses are suspected.

5.1.5.2 Transabdominal Ultrasound

Ultrasound is noninvasive but is operator dependent and has limitations in obese patients. Sensitivity in detecting clinically occult hernias in a non-acute presentation is 33%, with a specificity of 100%, and patients with normal ultrasound findings should be considered for further investigation, but hernias with characteristic clinical features need no additional investigation [50]. It is important because it can reveal the contents of the hernia sac that can include gynecological organs or tissues (part of the uterus, uterine fibroids, etc.), and then gynecologic/obstetric intraoperative consultation is mandatory. Also, it can find the cause that needs only conservative therapy like round ligament varicosities (see Sect. 5.2.5.1).

5.1.6 Treatment

Pregnant patients presenting with asymptomatic reducible groin or umbilical hernias during pregnancy can safely be managed nonoperatively until postpartum. All these patients have uncomplicated deliveries [51]. Elective, postpartum hernia repair provides similar results to the nonpregnant population [51]. In general population, a higher proportion of emergency operations is carried out in women (16.9%) than men (5.0%), leading to bowel resection in 16.6 and 5.6%, respectively. During reoperation, femoral hernias were found in 41.6% of the women who were diagnosed with a direct or indirect inguinal hernia at the primary operation. The corresponding proportion for men was 4.6% [52]. These data should be kept in mind when operating on a pregnant patient.

If uterine fibroids are found in the hernia sac, there are two options: (1) if there is a sign of bleeding, hematoma, or necrosis (degeneration) due to vascular insufficiency, uterine fibroids should be excised; (2) if aforementioned changes are not present, uterine fibroid is pushed into the abdomen and hernia repaired. Therefore, obstetric consultation is mandatory if imaging diagnostic modalities show gynecologic organs or pathologies in the hernia sac.

There are two unresolved issues: (1) the use of prosthetic materials during pregnancy and (2) the role of the abdominal binder during the postoperative period during pregnancy.

5.1.6.1 Perioperative Management

The rate of serious postoperative complications is lower under local anesthesia, including fewer postoperative analgesic requirements and fewer micturition problems [53] (see Chap. 23). In emergency settings, it is better to perform the operation under general anesthesia due to possible unexpected intraoperative findings.

5.1.6.2 Inguinal Herniorrhaphy During Cesarean Section

One of the earliest descriptions of simultaneous surgeries in general population was made by Ferguson in 1908 [54]. It was not uncommon at that time to remove the uterus, salpinx, appendix, or prostate during a hernioplasty. In the 1980s, surgeons cautioned that simultaneous surgical treatment of more than one disorder was associated with increased risk and cumulative postoperative complication rates up to 50% than for single procedures [55]. It has been suggested that combined hernioplasty and open prostatectomy may increase the risk of infection as a result of combining clean and contaminated surgeries [56]. Advances in anesthetic drugs and surgical techniques, particularly the introduction of minimally invasive methods, have made combined surgical procedures more popular in general population.

Even in elective settings, dilemma exists whether to perform herniorrhaphy in a pregnant patient with an abdominal wall hernia and an indication for CS. The combination of inguinal hernia repair with elective CS was first reported in 1987 by Altchek and Rudick [57]. CS in a woman with an umbilical hernia, inguinal hernia, and incisional hernia after midline or paramedian laparotomy can be made with a single incision and operation time less than 120 min [58]. In patients with bilateral inguinal hernia, the procedure is significantly prolonged [5]. This corresponds to wound infection rate in general population: in operations lasting 61–90 min (4.0% infection rate), as opposed to 91–120 min (6.2%) or greater in operations longer than 120 min (8.0%) [59]. Therefore, wound infection is similar in both groups, 4%, and hospital stay did not differ significantly [58]. CS with repair of more distant hernias requires combined procedures with separate incisions and significant prolongation of operation. Longer duration of operation is associated with an increase in wound infection rates [59].

> Prolonged hospitalization and an increase in complication rate were not observed in the combined procedures with a single incision.

No complications were recorded during the perinatal and follow-up periods. There are no recurrences observed [5] or are extremely rare [58].

The practical benefits are obvious: a 2-in-1 operation, single incision, single anesthesia, and single hospital stay confer valuable advantages for both the patient and hospital in terms of time, cost, convenience, and avoidance of the separation of mother from her newborn baby entailed by a separate operation. The length of full recovery is not different in the combined surgery patients compared with those who received a CS alone [60]. Patients expressed subjective satisfaction and recommended the combined procedure, primarily because it saved time and obviated the need for child care during reoperation.

Surgical Technique

Simultaneous CS and inguinal hernia repair are performed using 10–12 cm Pfannenstiel incision along the pubic hairline centered over the pubic symphysis. The superficial and deep fascias are divided and the rectus sheath exposed. An

incision is made in the rectus sheath with the parts directed superiorly and laterally at 30° from the skin incision, parallel to the inguinal canal and up to the lateral border of the rectus muscle. The rectus and pyramidalis muscles are exposed and separated in the midline (Fig. 5.15a–c). This provides excellent exposure of the uterus. A standard CS is performed.

After delivery, a surgical team performs the anterior or preperitoneal inguinal hernioplasty. Anterior inguinal hernioplasty is performed by dissecting the subcutaneous surface along the inferior aspect on the Pfannenstiel incision. The external oblique aponeurosis is exposed over the inguinal canal, and the superficial inguinal ring is identified (Fig. 5.15d). The external oblique aponeurosis is incised, and the inguinal canal is entered. The hernia sac is explored for indirect or direct hernias. There are no studies whether a tension-free Liechtenstein hernioplasty using a polypropylene mesh sutured with prolene 2/0 or Bassini repair is better. The external oblique incision is closed with 3-0 absorbable suture.

During preperitoneal inguinal hernioplasty, the rectus muscle is retracted up and the preperitoneal space dissected laterally, extending through the internal inguinal ring. While the Pfannenstiel incision is horizontally placed through rectus abdominis sheet, it leaves the muscle intact and enters the peritoneal cavity

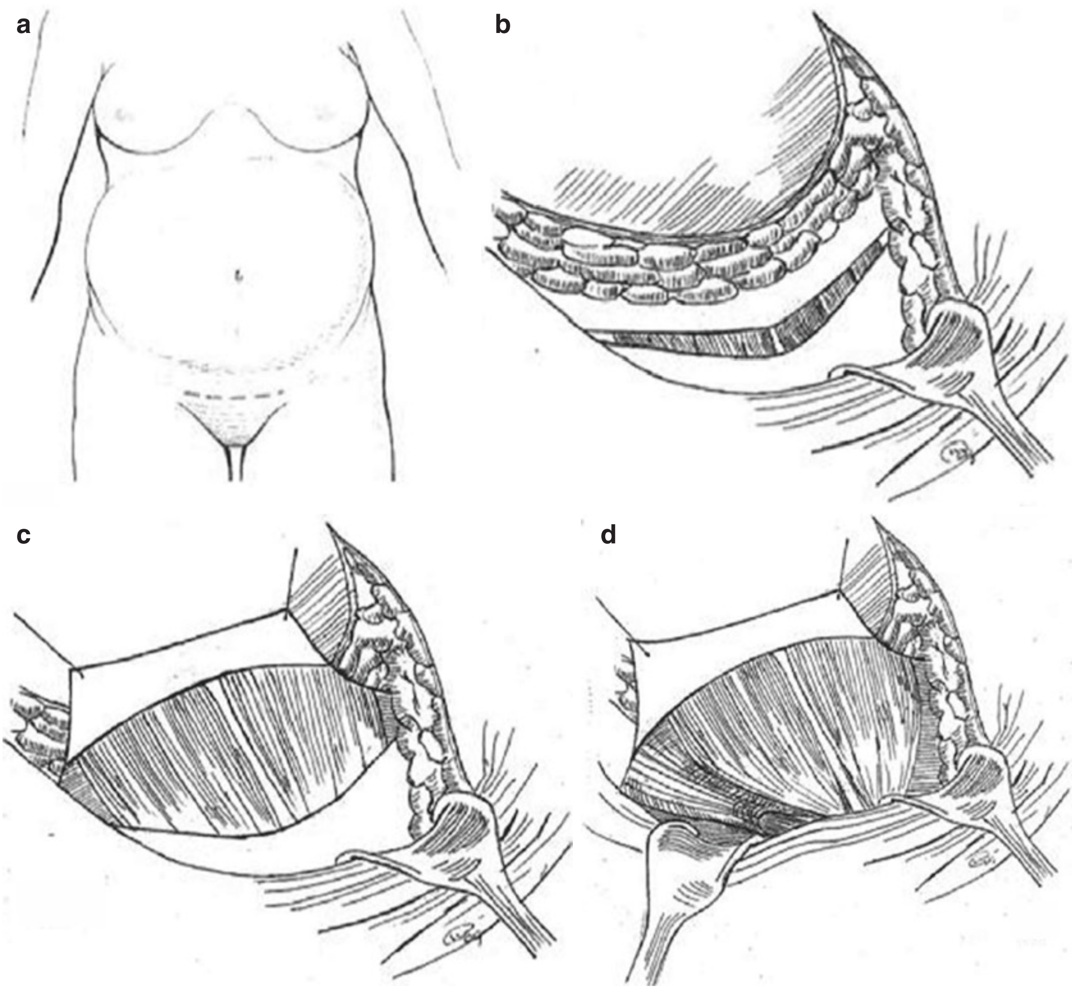

Fig. 5.15 (**a**) Skin incision; (**b**) U-shaped incision on rectus sheath; (**c**) dissection of superior leaflet on rectus sheath; (**d**) exposition of external oblique aponeurosis over the inguinal canal. Reproduced with permission from [60]

between left and right rectus abdominis muscles. At this level of the abdominal wall, there is no posterior rectus sheet; hence retraction of the muscle enables direct preperitoneal access to Retzius space followed by entrance in the space of Bogros. After the identification of a hernia and reduction of its content, preperitoneal iliopubic tract repair is performed as described by Nyhus [61]. Continuous 2–0 polypropylene sutures are placed too close to the posterior wall of the inguinal canal till to internal ring, and then a final 1 or 2 interrupted sutures are placed at the lateral edges of the ring. The operation could be done in general or spinal/epidural anesthesia.

5.1.7 Prognosis

The postoperative course of incarcerated inguinal hernia depends on the content of the hernia sac and duration of the incarceration. The most important complication is hernia recurrence. The data for postherniorrhaphy pain or surgical site/mesh infection are not known for patients operated during pregnancy.

5.1.7.1 Hernia Recurrence

Recurrence in the general population is 1–20% [62]. Recurrence rates are not known for inguinal hernioplasty during pregnancy. It is often secondary to deep infection, undue tension on the repair site, or tissue ischemia as in nonpregnant patients. The high postoperative morbidity rate in nonpregnant women compared with men is due both to their high proportion of a femoral hernia and to an increased risk for the emergency procedure in all types of groin hernias [3]. Because femoral hernias are more frequent in recurrent hernias than in primary hernias, it has been suggested that femoral hernias may be overlooked during repair of inguinal hernias. Possible reasons for the high rate of emergency operation in femoral hernias are no or vague symptoms prior to incarceration, and diagnostic difficulties, even at incarceration [3]. McEntee et al. concluded that strangulated hernias were misdiagnosed by the general practitioner in 33% of patients and by the hospital registrar in 15% [63]. Still the unanswered question is whether laxity of the abdominal wall and the presence of an enlarged, hypertrophied uterus could weaken a repair. Studies even with simultaneous operations such as hernioplasty and CS [5, 57] did not document higher recurrence rates. It should be interpreted with caution due to a small number of patients in all published studies.

5.1.7.2 Postherniorrhaphy Pain

Postoperative groin pain (inguinal neuralgia and inguinodynia) is common. It follows the distribution of the regional nerves, including the ilioinguinal, iliohypogastric, lateral femorocutaneous, and genital branch of the genitofemoral nerve. Nerve injury is usually due to the entrapment of a portion of the nerve in the mesh or suture line.

5.1.7.3 Surgical Site/Mesh Infection

Infection of the hernia wound or mesh is an uncommon postoperative complication but represents another etiology of recurrence. In specialized hernia centers, the incidence of wound infection is <1%. When an infection does occur, skin flora is the most likely etiology, and appropriate gram-positive antibiotics should be initiated. If mesh (nonabsorbable) is present, most postoperative groin hernia infections could be treated with the aggressive use of antibiotics after the incision is opened and drained expeditiously [64]. Mesh removal is rarely indicated.

5.2 Umbilical Hernia

5.2.1 Incidence

Approximately 5–7% of all primary hernias in the adolescent/adult general population are umbilical [65]. An infantile umbilical hernia is the result of an abnormally large or weak umbilical ring that fails to close in an otherwise normal abdominal wall. The herniation is typically at the umbilicus, but it may be above (supraumbilical) or below that level (infraumbilical). The defect is covered by the skin. The umbilical ring is not covered by fat. The adult umbilical hernia may be the result of untreated infantile hernias that fail to close spontaneously. Only 10.9% of

adults with umbilical hernias recalled having hernias from childhood with a male to female ratio 1:1 [66]. Umbilical hernias (protrusions of >5 mm and diameters of >10 mm from the abdominal skin surface) are present in about 15% of pregnant West African women [67]. Among the tribes of the Plateau region of Northern Nigeria, umbilical hernias are very common, and many regard the protruding umbilicus as a thing of beauty. Some even proudly adopt the name “Mai cibi”—the possessor of an umbilicus [68]. Incidence in the developed world is 0.2% [4]. An early description of an umbilical hernia in pregnancy was in 1907 [69] by Ernest F. Robinson (Fig. 5.16) and the first incarcerated umbilical hernia in the seventh month of pregnancy by Coley and Hoguet in 1918 [70].

Fig. 5.16 Ernest F. Robinson (1872–1945) upon settling in Kansas City became chief surgeon for two railroad companies and, in 1905, joined the University of Kansas School of Medicine as a Professor of Surgery—an association that lasted until 1909. Reproduced with permission from [71]

5.2.2 Etiopathogenesis

5.2.2.1 Risk Factors

Mostly, adult hernias present de novo pathology because of either a weakness of the abdominal wall or an increase in abdominal pressure (as in pregnancy), cirrhosis, ascites, obesity [65], or a combination of several pathologic processes. The neck of an umbilical hernia is usually quite narrow (1–2 cm) compared with the size of the hernia mass, and strangulation is, therefore, common [65, 72]. In some patients, especially undeveloped or developing countries, the umbilical hernia is treated by the application of traditional herbal medicines which often cause inflammation, necrosis, and sometimes gangrene of the skin resulting in decubitus ulcers which may precipitate spontaneous rupture of a hernia [73].

Incarceration/strangulation depends mostly on the angle at which the long axis of the presenting part meets the plane of the hole. In congenital umbilical hernias, it is usually 90^{o}, but in inguinal hernias the angle is more acute; in acquired adult umbilical hernias, the hole is made by the stretching of the interdigitating fibers, and the resulting hole is likely not to be always at right angles to the force producing it, and therefore incarceration/strangulation sometimes occurs.

5.2.2.2 Uterine Fibroids

Uterine fibroids can be pedicled or sessile. Most uterine fibroids have a pedicle, and these can easily enter any hernia sac if smaller than the hernial orifice. Hypothetic mechanism of the incarceration of fibroids without pedicle is as follows. Since the free movement of such fibroids is very limited, their risk of incarceration is much lower than those of their pedicled counterparts. The progression of pregnancy makes the fibroid displace cranially onto the anterior wall of the uterus. During this process, compression of the uterus in the posterior to the anterior direction in the abdominal cavity may cause the fibroid to be easily entrapped in the umbilical opening of the hernia sac. The incidence of fibroids during pregnancy (see Chap. 18) is 1–4% [74].

5.2.2.3 Gravid Uterus

Finding a gravid uterus in an anterior abdominal wall hernia is rare and is usually found in multiparous patients [5, 73, 75–77]. Gravid uterus in wide umbilical hernia causes direct pressure and enlargement of umbilical ring. When the uterus fills up a hernia and during further pregnancy enlarges, it becomes incarcerated in a hernia.

5.2.2.4 Laparoscopic/Single Port Surgery

In the recent decades due to the development of laparoscopic/single port surgery, postoperative hernia after supra-, infra- or transumbilical incisions can be mistaken for an umbilical hernia. It could be differentiated by history taking and evidence of surgical scars.

Fig. 5.17 A multiparous woman with a huge umbilical hernia with skin necrosis over the umbilicus in 38-week pregnancy presented in labor. She had vaginally delivered her previous children. She had never had abdominal operation. Reproduced with permission from [76]

5.2.3 Clinical Presentation

There are several types of presentation:

- Incarcerated umbilical hernia
- Incarcerated gravid uterus in an umbilical hernia (Fig. 5.17)
- Skin ulceration/skin necrosis overlaying umbilical hernia (Fig. 5.17)
- An umbilical hernia with spontaneous skin ruptures at the point of skin necrosis (Fig. 5.18)

Fig. 5.18 Spontaneous rupture of large umbilical hernia with eviscerated vital omentum. Reproduced from [78] with permission

The last two presentations are most commonly seen in patients with the gravid uterus in the umbilical hernia sac. There are two parts of the diagnostic process. First is the definition of (incarcerated) an umbilical hernia itself, and second is the definition of the contents of the hernia sac, both important for the type of treatment. Diagnosis is definitive if there is a dilated umbilical ring with or without contents in a hernia sac. If incarceration is present, symptoms depend on the incarcerated organ and duration of incarceration: incarcerated bowel causes vomiting, abdominal distention, and absence of stool and flatus passage (see Chap. 7); incarcerated uterine fibroid or greater omentum causes only pain and local tenderness. If the bowel becomes necrotic, perforation ensues into the surrounding tissue of the abdominal wall with erythema and edema of the skin overlying the hernia. This should be differentiated from the skin ulceration/skin necrosis due to the long-standing pressure of mostly enlarged gravid uterus (Fig. 5.17). The gravid uterus can be defined as palpation of smooth surface and fetal parts in it.

5.2.4 Differential Diagnosis

5.2.4.1 Omphalitis/Periumbilical Abscess

History taking is important because in omphalitis there is no previous hernia and, in a periumbilical abscess, there is often the history of the cleansing

of umbilicus with small sticks which cause skin abrasions with inoculation of bacteria. Furthermore, systemic symptoms are rarely present in omphalitis and periumbilical abscess.

5.2.4.2 Umbilical Endometriosis

Incidence

Cutaneous EM (CEM) accounts for less than 5.5% of all EM cases [79–81]. Less than 30% of CEM cases appear in the absence of prior surgery and are then referred to as primary or spontaneous CEM [79–81]. Cutaneous EM of the umbilicus is also known as *Villar nodule*, with reference to the physician who first described it in 1886. Cutaneous EM can develop spontaneously during pregnancy and is then most often located on the umbilicus [82, 83]; it may regress spontaneously after delivery [83]. Umbilical EM (UEM) accounts for up to 30–40% of all CEM cases [79, 80]. Up to 2008, 234 cases of UEMs have been described and only two of UEM in pregnancy [82, 83].

Clinical Presentation

It manifests as a rubbery or firm nodule ranging in size from some mm to 6–9 cm (mean 2–2.5 cm). Its color varies from red and blue to brown-black, depending on the amount of hemorrhage and the penetration depth of ectopic endometrial tissue. Occasionally, the nodule is flesh colored [84]. It is usually single and often multilobulated (Fig. 5.19), although multiple discrete nodules may be present [85]. Clinical symptoms include tenderness, pain, bleeding, swelling, and growth correlated with the menstrual cycle. However, not all symptoms are present in a given patient and some patients are totally asymptomatic [86]. It is essential to point out that cyclicity is not always demonstrable and is not essential for diagnosis [87]. Umbilical EM may be associated with an umbilical hernia [88, 89]. When UEM is associated with pelvic EM, general symptoms such as dysmenorrhea and dyspareunia may be present.

Diagnosis

The diagnosis of CEM can be suspected clinically on the basis of the clinical appearance and a good history but relies mainly on histopathological

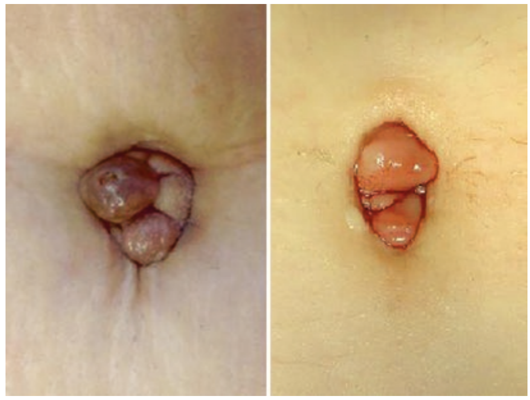

Fig. 5.19 (*Left*) A multilobulated, *red-brownish* nodule that had developed 10 years earlier over the umbilicus, 2 years after the delivery of a single healthy baby. Reproduced from [90] under the CC BY 2.0; (*right*) Caucasian, nulligravid woman without previous endometriosis or umbilical operation. Reproduced with permission from [82]

examination (Fig. 5.20). Other helpful imaging methods include dermatoscopy, MRI, and ultrasonography. Dermatoscopic findings of EM include a homogenous reddish pigmentation with small, well-defined, globular structures of a deeper hue, termed *red atolls* [91]. The findings in MRI include a low signal on T1 weighting and a low or high signal on T2 weighting, depending on the presence or lack of hemosiderin [86]. Ultrasonography and CT are more accessible but not as sensitive as MRI. Fine-needle aspiration cytology results may be inconclusive [30, 81]. Serum CA-125 levels may be increased [83], but are not specific for EM.

Gynecologic examination and hormonal evaluation prior to excision of CEM could detect an associated pelvic EM. Abdominal and transvaginal ultrasonography or abdominal/pelvic MRI should be performed in all asymptomatic patients [30, 81, 84, 92] because the presence of extrapelvic endometriosis has been reported in many organs and in up to 15% of the patients with endometriosis [79, 93]. It has been reported that up to 40% of patients with extragenital endometriosis present with umbilical lesions.

Treatment

The treatment of CEM in general nonpregnant female population is mainly surgical (Fig. 5.21), preferably performed at the end of the menstrual

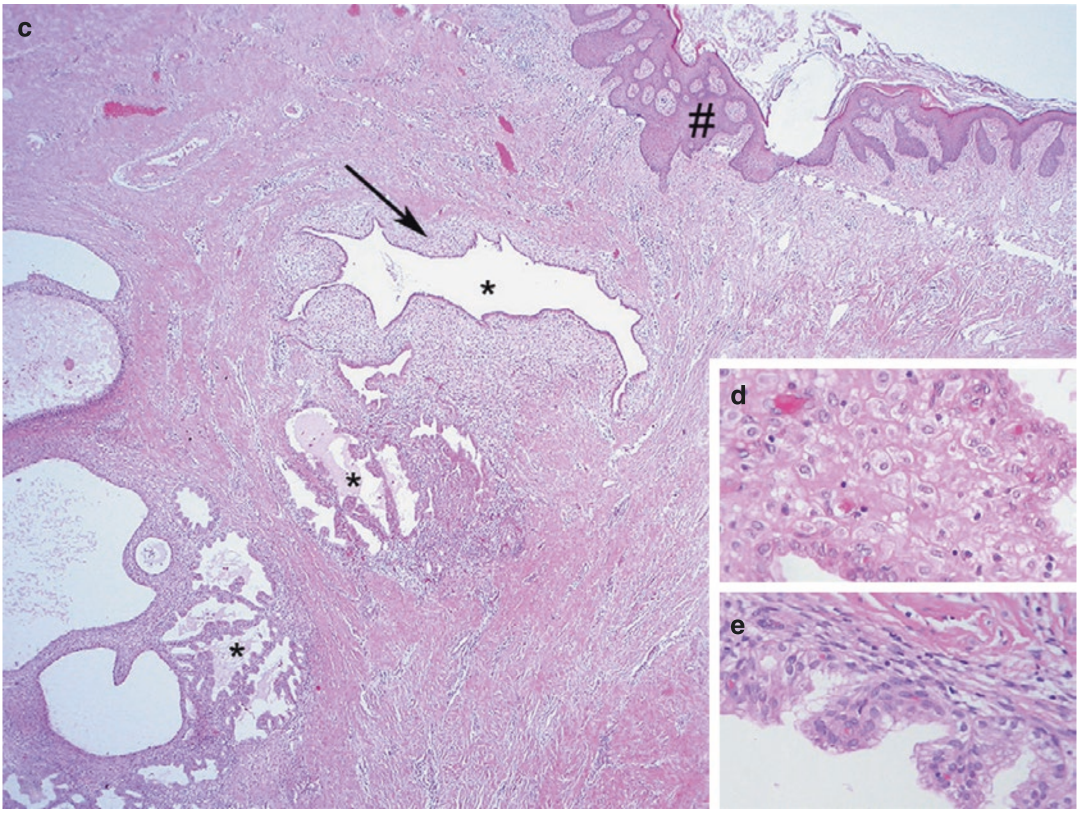

Fig. 5.20 Endometriosis of the umbilicus. (**c**) The partial decidual reaction of the stroma. Histologic examination demonstrated endometrial glands (*) surrounded by endometrial stroma (*arrow*) beneath the squamous epithelium of the skin (#) (hematoxylin and eosin ×10). (**d**) Gestational hyperplasia and (**e**) focal Arias-Stella reaction of the endometrial epithelium as signs of pregnancy (hematoxylin and eosin ×200). Reproduced with permission from [82]

cycle when the lesion is small in order to achieve a minimal excision [94]. The technique of removal varies depending on the size and extent of the lesion, from simple excision with wide margins (Fig. 5.22) under local anesthesia to laparoscopic excision en bloc of the umbilicus [84] with concomitant pelvic surgery if pelvic EM is confirmed (see further text). A polypropylene mesh may be necessary to prevent the development of a hernia if the defect in the rectus sheath is large [81]. In nonpregnant population, treatment with gonadotropin-releasing hormone agonists, danazol, and monophasic contraceptive pills can be given in order to reduce tumor size before excision or provide relief from the symptoms [79, 92]; these are insufficient as sole treatments [92] and may lead to incomplete excision [81]. Whether laparoscopic examination for extrapelvic endometriosis should be systematically performed is still debated [30, 81, 84, 92]. All these principles should be applied to pregnant population except adjunctive hormonal therapy which is questionable in pregnancy. If pregnancy is advanced and there is no significant progression in terms of significant pain, bleeding, or enlargement, the treatment can be delayed after the childbirth due to benign nature of the disease.

Prognosis

The prognosis of CEM in general female population is good. Recurrences are uncommon if excision is performed with clean and wide margins. However, malignant transformation has been reported in 0.3–1% of scar EM and should be suspected in the case of rapidly growing or recurrent

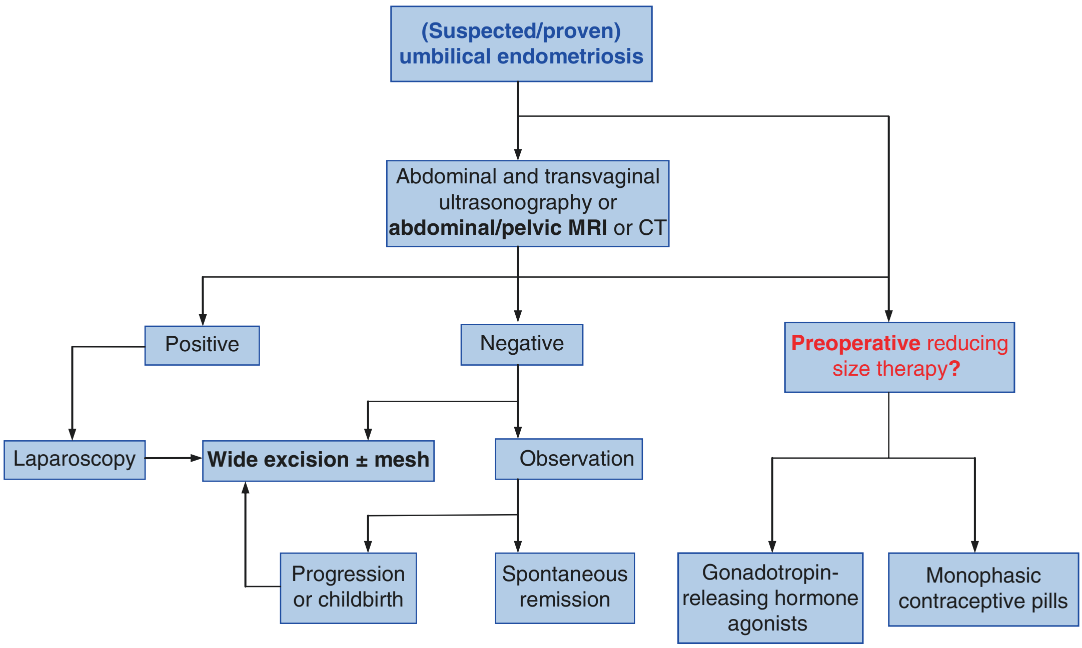

Fig. 5.21 Treatment algorithm for umbilical endometriosis. During pregnancy preoperative hormonal therapy is questionable and not studied yet

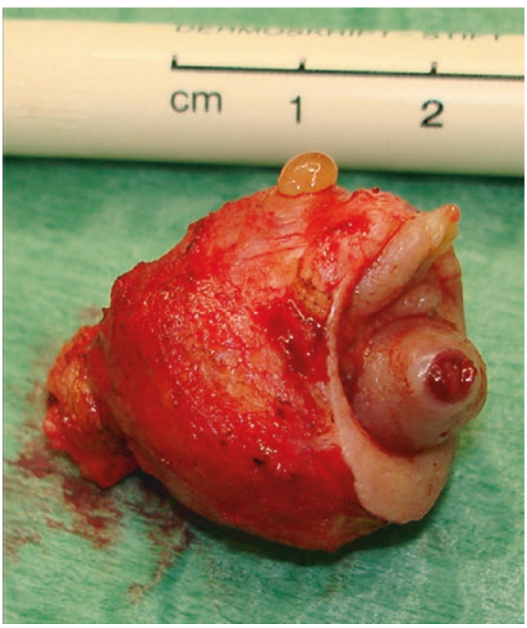

Fig. 5.22 Completely excised endometriosis of the umbilicus. Reproduced with permission from [82]

lesions [95]. The most common histological subtype in malignant transformation is endometrioid carcinoma (69%) followed by clear-cell carcinoma (13.5%), (adeno)sarcomas (11.6%), and serous carcinoma [95]. Due to the extremely small number of patients in pregnancy, the prognosis is unknown but published cases claim excellent results [82, 83].

5.2.4.3 Umbilical Endosalpingiosis

Endosalpingiosis is a rare clinical entity that describes the ectopic growth of Fallopian tube epithelium [96]. Endosalpingiosis, endometriosis, and endocervicosis constitute the triad of nonneoplastic disorders of the Müllerian system. These pathologies are found in isolation but are more commonly found in association with one another. The term endosalpingiosis was employed first by Sampson et al. in 1930. Under that term, the authors designated any unusual growth and invasion of tubal epithelium in tubal stumps, in subjects who had undergone previous salpingectomy or tubal sterilization [96]. There are no published cases of umbilical endosalpinginosis during pregnancy.

Pathogenesis

The different theories for the pathogenesis of endosalpingiosis are similar to those for endometriosis, since those two entities, together with endocervicosis, constitute the nonneoplastic disorders of the Müllerian system. The different models can be traced back to two basic ideas. One

group of theories is based on the fact that endometrial cells (or their precursors) are transported by various routes (transtubal, hematogenous, lymphogenous, or direct apposition) and implanted in the affected organ. The other group of theories suggests that Müllerian ectopias are the result of metaplastic processes in the target organ (coelomic metaplasia theory, secondary Müllerian system) or from scattered embryonic rest [97].

Clinical Presentation

These lesions appear as nodules of the umbilicus and are usually brownish in color. The main symptoms (besides the esthetic) are pain and size fluctuation with menstruation. The lesion can be present after gynecologic procedures [98] or can develop spontaneously [99].

Diagnosis

The diagnosis of these pathologies is made histologically. In the case of endosalpingiosis, pathology confirms the presence of a tubelike epithelium containing three types of cells: ciliated, columnar cells; non-ciliated, columnar mucous secretory cells; and the so-called "intercalary" or "peg" cells [98].

Treatment

The treatment of choice is surgical excision. Excision should be done under local anesthesia, in order to minimize morbidity and hospitalization if small. However, the patient has to be notified that in the case of a reappearance of abdominal pain (especially in the lower quadrant), a laparoscopy should be performed in order to exclude abdominal endometriosis.

5.2.5 Diagnosis

5.2.5.1 Plain Abdominal X-Ray

Plain abdominal X-ray can confirm or exclude bowel obstruction, but if a clinical diagnosis of incarcerated umbilical hernia is evident, it is not necessary, avoiding the risk of fetal exposure.

5.2.5.2 Transabdominal Ultrasound

Abdominal ultrasound is diagnostic in doubtful cases to exclude other possible etiologies of painful periumbilical lumps (see Sect. 5.3.5) or to

Fig. 5.23 Transabdominal ultrasound of a 30-year-old woman at the 32nd gestational week of her first pregnancy showed hypoechoic, heterogeneous mass (uterine fibroid) measuring 28 × 21 mm within the umbilical hernia sac. Reproduced with permission from [72]

confirm or exclude the presence of the bowel in the hernia sac. Incarcerated uterine fibroids can be detected as a firm, hypoechogenic mass within the umbilical sac (Fig. 5.23).

5.2.6 Treatment

Therapeutic goals consist of several parts. First is the management of hernial contents which can be of various origins and sometimes need additional treatment. Second is the treatment of a hernia itself, and third is to treat the cause of the herniation if applicable. Incarceration and strangulation are considered relatively uncommon, but when they do occur, these complications are responsible for 10–20% of the indications for umbilical hernia repair [100]. One of the first published cases strangulated umbilical hernia in pregnancy is by Coley and Hoguet in 1918 [70] and ruptured umbilical hernia during pregnancy by Bruce Kenneth Young (Fig. 5.24) from 1965 [100]. Umbilical hernias in adults do not close spontaneously; slow enlargement over a period of years is common, and strangulation is much more frequent than in pediatric umbilical hernias; therefore elective operation is mandatory at a presentation in the adult population.

In elective and emergent settings, as in the general population, the recurrence rate correlates with the body weight and width of the hernia orifice. The recommendations for mesh use in umbilical hernia repair are:

Fig. 5.24 Bruce Kenneth Young from NYU Langone Medical Center published one of the first cases of ruptured umbilical hernia in pregnancy. Reproduced with permission from NYU Langone Medical Center webpage [101]

- BMI >30 kg/m^2
- hernia orifice >3 cm

A mesh repair has significantly lower recurrence rate in the general population. However, when the orifice is in the range of 2–3 cm, the decision to use mesh should be made on the basis of individual variations. Laparoscopic repair is an alternative to the open mesh repair of an umbilical hernia. Irreducible umbilical hernias without symptoms should be repaired on a semi-urgent basis before the enlarging uterus causes possible organ (most often small bowel) strangulation. A symptomatic irreducible umbilical hernia is an absolute indication for urgent operation. Skin ulceration without incarcerated hernia is the semi-urgent situation when frequent controls are necessary, and if progression to skin necrosis or skin rupture develops, then the urgent operation is mandatory (Fig. 5.17).

Small incarcerated umbilical hernias without bowel obstruction can be operated under local anesthesia minimizing the rate of anesthetic effects on both mother and fetus.

The role of the abdominal binder during the postoperative period in pregnancy and puerperium is not known.

5.2.6.1 Anesthetic and Perioperative Management

See Chap. 21.

5.2.6.2 Obstetric Management

Complications

Multiple complications have been reported in association with pregnancies in anterior abdominal wall defects. These include miscarriage, premature labor, intrauterine hemorrhage, intrauterine growth retardation, intrauterine death, rupture of the lower uterine segment, and death [77, 102].

Prevention and Treatment of Preterm Labor

See Chap. 23.

5.2.6.3 Early Postoperative Complications

The suture repair of a large defect may result in tissue tension which is associated with high recurrence. In addition, such repair may cause raised intra-abdominal pressure which is additionally exaggerated in advanced pregnancy increasing the possibility of abdominal wall suture rupture. Maternal respiratory complications include atelectasis and pneumonia that could be prevented or minimized by (1) hernia repair without tension mostly with mesh repair and (2) chest physiotherapy and early ambulation.

5.2.6.4 Umbilical Hernioplasty During Cesarean Section

Combined procedure could be done in elective or emergent settings. Only several cases of the combination of umbilical hernia repair with gynecologic surgery or CS is documented [5, 58, 60]. The practical benefits are a 2-in-1 operation, with a single incision, single anesthesia, and single hospital stay, conferring valuable advantages for both the patient and hospital in time, cost, and convenience, not to mention avoiding the separation of the mother from newborn entailed by reoperation. The intraoperative difficulty of mesh fixation and to a lesser extent primary suture repair is the main problem, which always requires assistance to achieve good traction. Proponents of postpartum hernia repair may argue that the combined procedure increases the complication rate, because of blood loss and wound infection resulting from the longer operation time, and prolongs hospitalization. Hernia repair prolonged the average duration of CS, but the time remained

within the normal range reported for hernia repair in the literature. In all patients undergoing paraumbilical hernia repair, operation times remained below 120 min with a wound infection rate of 4.2% [58]. Other study confirmed these results with duration of combined procedure of 50 ± 7 min compared to 37.4 ± 12.6 min for CS alone [60]. No complication was recorded during the perinatal and follow-up periods, and no recurrences were observed. In the third study with three patients, there was even no prolongation of operation time. Unfortunately, the diameter of an umbilical hernia and the type of the procedure for umbilical hernia repair were not mentioned [5].

Surgical Technique

The surgical technique consists of standard CS and umbilical hernia repair with the technique depending on the diameter of the umbilical defect. Mesh is placed when the defect is more than 3 cm [58]. Anesthesia could be general or epidural/spinal. CS is conducted as follows: the skin is disinfected with povidone-iodine, a Pfannenstiel skin incision is made in the lower crease, the fetus is delivered, and the uterine wound is closed, all the while maintaining good hemostasis. Patients receive antibiotic prophylaxis in the form of i.v. cefotaxime 1 g after placental extraction.

For umbilical hernia repair, a Kocher clamp is placed in the middle of rectus abdominis sheet at the edge of the upper abdominal flap. The flap is retracted superiorly to expose the peritoneal aspect of the umbilical defect. A vertical incision is made in the peritoneum underlying the umbilicus, and the caudal edge of the defect is identified by palpation. A second Kocher clamp is applied to this edge for traction and exposition of the defect. The assistant held the clamp in place, while the surgeon approximated the edges of the fascia with a continuous 2-0 polypropylene suture, starting at least 1 cm caudal to the defect and ending 1 cm cranial to the superior edge of the defect (or a total of 4 cm from the starting point) then downward with the same suture for second row, and ends are tied. Due to higher collagen content, it is easy to palpate the caudal border of the umbilicus, whereas the cranial border is indistinctive due to attenuated collagen structure and not easily palpable. If the suture line is too short, a partial wall defect may remain which means missed hernia; hence even if the defect cannot be palpated well, approximation of a 4 cm part of the midline abdominal wall around the defect is made. Subsequently, the peritoneal layer overlying the defect was closed. Closure of the CS wound is done in standard fashion.

5.2.6.5 Uterine Fibroids

Most of the uterine fibroids in pregnancy are asymptomatic [100], and no treatment is needed if intramural and subserosal fibroids of 3 cm or smaller are present. Only 10% of previously diagnosed fibroids cause complications during pregnancy or delivery. Although some complications are reported as a result of changes in the anatomical localization of the fibroids during pregnancy, the most common complication is a pain due to degeneration [100]. The first report of incarcerated umbilical hernia with a fibroid during pregnancy was by Ehigiegba and Selo-Ojeme in 1999 [100]. As a general rule if there are no signs of bleeding, hematoma, or necrosis or rupture, the fibroids are not resected and are gently pushed into the abdominal cavity (Fig. 5.25) after which umbilical hernia repair is performed [72]. If aforementioned changes are present, myomectomy and then hernioplasty should be performed [100]. If the fibroids are not resected, obstetrical ultrasonography can be performed on the first postoperative day for

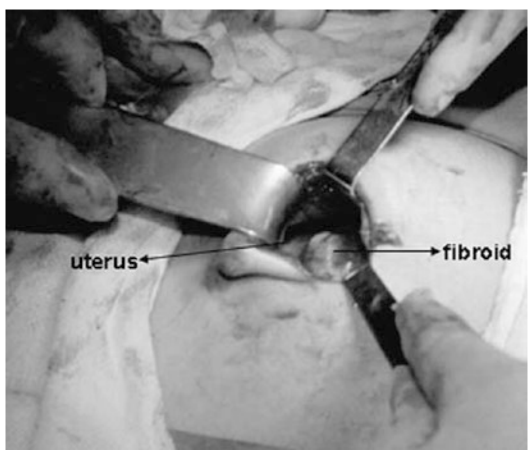

Fig. 5.25 The edematous, subserosal sessile fibroid without signs of bleeding, hematoma, or necrosis seen from the umbilical incision which was not resected. Reproduced with permission from [72]

evaluation of the uterine fibroids, the uterus, and the status of the fetus [103].

5.2.6.6 Gravid Uterus

> *When the patient stood upright the fundus of the uterus was at a lower level than the symphysis pubis. Per vaginam the cervix could not be reached. The uterus was thus almost completely upside down and it was acting as a lever with the lower edge of the hernial orifice as the fulcrum.*
>
> Thomson SW, 1962

The first descriptions of gravid uterus in an umbilical hernia were reported by Thomson in 1962 (Fig. 5.26) [68] and Wydell in 1963 [104]. Less than 20 cases of gravid uterus in an umbilical hernia have been published. It has been suggested that the laxity of the abdominal wall and the presence of an enlarged, hypertrophied uterus could weaken a repair. Despite these theoretical concerns, different types and locations of hernias have been successfully operated as part of the CS (Fig. 5.27) with no increase in wound infection rates and no recurrences (see Sects. 5.1.6.2 and 5.2.6.4).

Fig. 5.26 The blanket which passes around the abdomen shows the lower limit of hernia neck. The level of the fundus can be gauged from that of the hand. Reproduced with permission from [68]

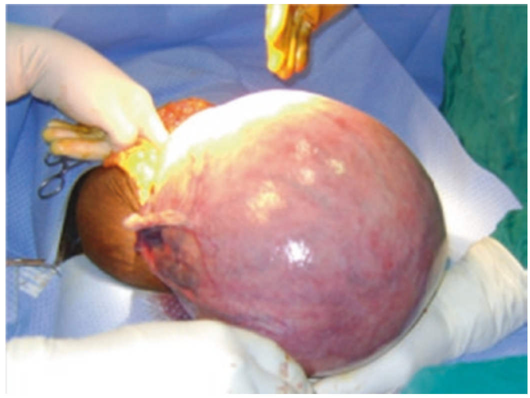

Fig. 5.27 Full-term pregnancy in the umbilical hernia. Cesarean section was performed followed by suture repair of giant umbilical hernia (mesh was not available during operation). Patient's repair was intact at follow-up >1 year after surgery; the baby was healthy and developing normally. Reproduced from [76] under the CC BY 2.0

> The recommendation is to repair an umbilical hernia containing gravid uterus after CS during the same operation. It eliminates potential bowel obstruction between pregnancies or gravid uterus incarceration in subsequent pregnancies.

Indications for mesh placement are the same as in nonpregnant population. Another indication for CS is described by Thomson when the upside-down position of the uterus in giant umbilical hernia prevents normal vaginal delivery: "When the patient stood upright the fundus of the uterus was at a lower level than the symphysis pubis. Per vaginam the cervix could not be reached. The uterus was thus almost completely upside down and it was acting as a lever with the lower edge of the hernial orifice as the fulcrum" [68]. There are several cases of ruptured umbilical hernias causing so-called *burst abdomen* (see Chap. 22). The suture repair of a large defect may result in tissue tension which is associated with high recurrence (see Sect. 5.2.6.3).

5.2.7 Prognosis

Prognosis for the fetus is excellent if the CS is performed before fetal distress occurs. Published cases do not have long-term follow-up; therefore, hernia recurrence rate is unknown. One of the first published cases of strangulated large umbilical hernia by Coley and Hoguet from 1918 resulted in wound infection and recurrence 8 months after the operation [70].

5.3 Epigastric Hernia

5.3.1 Incidence

An epigastric hernia is a hernia in the midline of the anterior abdominal wall between the umbilicus and the xiphoid and through a defect in the linea alba. It accounts for 1% of all hernias in general population, but the true incidence may be higher because, as the majority of them are asymptomatic, many patients do not seek medical advice. There are only two reports during pregnancy including three patients [105, 106].

5.3.2 Clinical Presentation

There can be a history of a reducible epigastric swelling. Swelling can be painless but can become painful and even irreducible over time. Obstructive bowel symptoms should be checked. Temperature measurement and hemodynamic stability should be check in addition to an obstetrical examination.

5.3.3 Differential Diagnosis

Differential diagnosis is almost the same as for an umbilical hernia (see Sect. 5.4.4). Expansive intra-abdominal pathology should be excluded, such as large uterine fibroids in advanced pregnancy.

5.3.4 Diagnosis

The diagnosis of an epigastric hernia, reducible or incarcerated, is almost always clinical. Hernias are mostly small, 2–10 cm above the umbilicus in the midline. Diagnostic imaging modalities are the same as for other anterior abdominal wall hernias (see Sect. 5.1.5).

5.3.5 Treatment

A proposed algorithm for the management of epigastric hernias in pregnancy is presented in Fig. 5.28. The algorithm is a combination of watchful waiting and emergency herniorrhaphy depending on the clinical presentation. In advanced pregnancy, uterus covers the defect minimizing the possibility of incarceration.

5.3.5.1 Anesthetic and Perioperative Management

See Chap. 21.

5.3.5.2 Prevention of Preterm Labor

See Chap. 23.

5.3.6 Prognosis

Prognosis is excellent due to easy clinical diagnosis and extremely rare incidence of incarceration in general as well as in pregnant population [105, 106].

5.4 Postoperative (Incisional) Hernia

5.4.1 Incidence

The incidence of an incisional or a postoperative hernia in general population is up to 18.7% at 10-year follow-up [100]. It must be differentiated from early wound dehiscence with evisceration with the incidence of 1–3% of laparotomies which requires immediate reoperation [100]. The incidence of a postoperative hernia is 3% following CS due to defective abdominal wound healing and herniation of gravid uterus through the abdominal wall [100] and is associated with midline incisions, the need for additional operative procedures, longer than usual administration of antibiotics and more potent antibiotics, presence

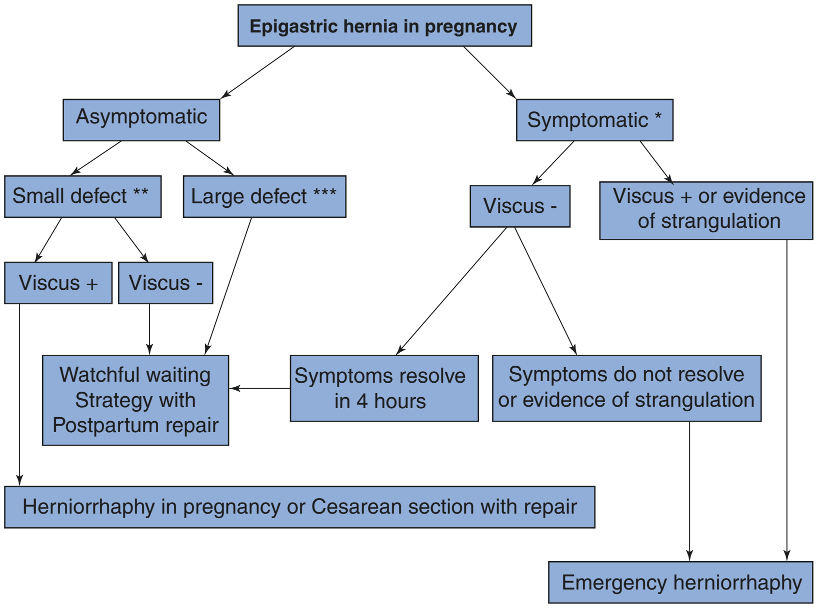

Fig. 5.28 Management algorithm for an epigastric hernia in pregnancy. * pain, irreducible, ** ≤2cm *** >2cm. Reproduced with permission from [105]

of postoperative abdominal distention, intra-abdominal sepsis, residual intra-abdominal abscess, wound infection, wound dehiscence, and postoperative fever [100]. The incidence of a postoperative hernia in pregnancy is unknown. There are only case reports regarding this condition. There may be several reasons for the condition's estimated low incidence. First, pregnant patients mostly represent young and healthy adolescents that have either been operated on successfully in the earlier neonatal or childhood period or were never operated on. Second, patients with incisional hernias who plan future pregnancy probably subdue to operation before pregnancy. Approximately ten cases of gravid uterus in an incisional hernia have been reported. The first case has been described in 1977 when a woman presented with pressure necrosis of a CS scar with protrusion of the gravid uterus through the wound [77].

5.4.1.1 Gravid Uterus

Herniation of a gravid uterus through an incisional hernia of the anterior abdominal wall is a serious condition due to the potentially severe maternal and fetal risks [107, 108]. It is rare because, by the time the uterus reaches the level of hernial aperture, it is usually too large to enter the hernial sac [109]. Also, the patients with such large defects seek help because such large incisional hernias are mostly symptomatic before conception. The first known case was published by Arthur Holmes in 1906 [110]. A search of the literature reveals only 15 reported cases of such hernias complicated by pregnancy, of which 8 developed incarceration with or without subsequent strangulation commonly after 4 months of gestation [73, 107–109, 111–120]. Infraumbilical vertical incisions performed for CS, especially with postoperative sepsis/wound infections, are the most common risk factors [73, 109, 113, 121]. Unfortunately, most CS in some parts of undeveloped/developing countries are carried out by nonspecialist general duty doctors who do not have any additional training in obstetrics and gynecology. It results with more infraumbilical midline incisions rather than the Pfannenstiel incision probably because it is easier to perform a CS through an infraumbilical midline incision [121]. However, transverse suprapubic incisions in contrast to the infraumbilical midline incisions have very low rates of an incisional hernia due to the orientation of the incision and to the forces acting on it [122].

5.4.1.2 Abdominal Wall Endometrioma

Abdominal wall endometrioma can be divided into *spontaneous abdominal wall endometrioma* and so-called *scar endometrioma*. Scar endometrioma occurs after operation including abdominal wall incisions most commonly after gynecologic operations when endometriosis has the highest possibility of occurrence. The most common site for extrapelvic endometriosis is the Pfannenstiel incision scar with an estimated incidence of 0.03–1% [38, 123–125], known as *Cesarean scar endometriosis*. Studies from India showed a much higher proportion after hysterotomy for midterm abortion than for CS: 71–74% and 4–6%, respectively [126, 127]. These studies were performed in countries in which abortion via hysterotomy was relatively common.

Early hysterotomy in pregnancy is the main risk factor for abdominal wall endometriosis.

5.4.2 Clinical Presentation

Clinical presentation is similar to incarcerated umbilical hernia (see Sect. 5.2.3). History (previous operations) and clinical examination (abdominal wall scars with a palpable defect in the abdominal wall and distention) are mostly sufficient for the diagnosis. Diagnosis of a gravid uterus in an incisional hernia is made by the history of a hernia between pregnancies, the presence of an unusual bulge in the abdomen with stretched skin [73, 109], and easily palpable uterus and fetal parts [73, 117]. Types of clinical presentation are similar to an umbilical hernia in pregnancy:

- Incarcerated incisional hernia
- Incarcerated gravid uterus in an incisional hernia
- Skin ulceration/skin necrosis overlaying incisional hernia
- An incisional hernia with spontaneous skin rupture at the point of skin necrosis

Excessive stretching of the skin could cause visible skin ulceration. If there is incarceration, the uterus would be irreducible without any other symptoms; if there is incarceration/strangulation of the uterus, the patient can have severe abdominal pain and vomiting [108, 111].

5.4.2.1 Gravid Uterus

Diagnosis of a gravid uterus in an incisional hernia is made by the history of a hernia between pregnancies, the presence of an unusual bulge in the abdomen with stretched skin [73, 109], and easily palpable uterus and fetal parts [73, 117]. In large hernias with the gravid uterus in advanced pregnancy, skin discoloration, excoriation, and ulceration could be found (Fig. 5.29). These skin changes are always present at the apex of pendulous herniation as a result of marked ischemia of the skin and subcutaneous tissue. This results from stretching of the skin aided by acute angulation of arteries supplying the tip of a hernia [128]. In some cases, the lie and presentation sometimes could not be ascertained. Fetal position and palpation are not possible in cases with polyhydramnios [120]. The reported incidence of incarceration is about 53%, and the uterus is irreducible with or without any other symptoms. If it progresses to strangulation, severe abdominal pain, vomiting, and even shock can set in [128].

5.4.2.2 Abdominal Wall Endometrioma

The classic symptoms of an abdominal wall endometrioma are cyclic or catamenial pain associated with a (painful) mass. However, cyclic pain is not a universal characteristic of the pain [126, 130, 131], some claiming in only 57% of patients. However, the presence of a mass (96%) or pain (87%) is a more common symptom. Other common signs and symptoms are bleeding from superficial lesions and lower abdominal pain [124, 126, 127, 132].

Physical examination should focus on determining if the patient has a fascial defect (hernia) and if the mass feels as if it were attached to the anterior fascia. No further studies are necessary for patients with a classic presentation [133]. Accurate preoperative diagnosis rate varies in range 20–50% [45, 126]. One of the possible

Fig. 5.29 Cesarean scar hernias in advanced pregnancy. Decubital skin ulcers are found in the lowest part of a hernia. Reproduced with permission from [128, 129]

explanations of this diagnostic failure is that the diagnoses were made almost always by general surgeons who were not so familiar with this entity.

5.4.3 Diagnosis

If in doubt, abdominal ultrasound examination could define a hernia and structures in the hernia sac. A rare but serious obstetric situation can present when a gravid uterus herniates into an anterior abdominal wall through an incisional hernia [117, 118]. Complications including strangulation, abortion, premature labor, accidental hemorrhage, intrauterine death, and rupture of the lower uterine segment could be confirmed by transabdominal ultrasound [118].

5.4.3.1 Gravid Uterus

Clinical diagnosis is straightforward (see Sect. 5.4.2.1). Imaging studies like abdominal ultrasound and abdominal MRI (Fig. 5.30) can assist in diagnosis [117, 119] or define a fetal position or direct or indirect signs of fetal distress.

5.4.3.2 Abdominal Wall Endometrioma

After thorough physical examination, no further studies are necessary for patients with a classic presentation [133]. On ultrasonography, the mass may appear hypoechoic and heterogeneous with scattered internal echoes (Fig. 5.8). Some of the masses appear completely solid but occasionally

Fig. 5.30 Sagittal abdominal MRI T2-weighted image showing gravid uterus with the fetus in the incisional hernia of the patient presented in Fig. 5.29. Reproduced with permission from [128]

some cystic changes may be seen (see Sect. 5.2.4.2) [38]. Endometriosis has no pathognomonic findings on CT, as appearances depend on the phase of the menstrual cycle, the proportions of stromal and glandular elements, the amount of bleeding, and the degree of surrounding inflammatory and fibrotic response (Fig. 5.31). Owing to the relatively vascular nature of these lesions, enhancement often occurs on CT scans with

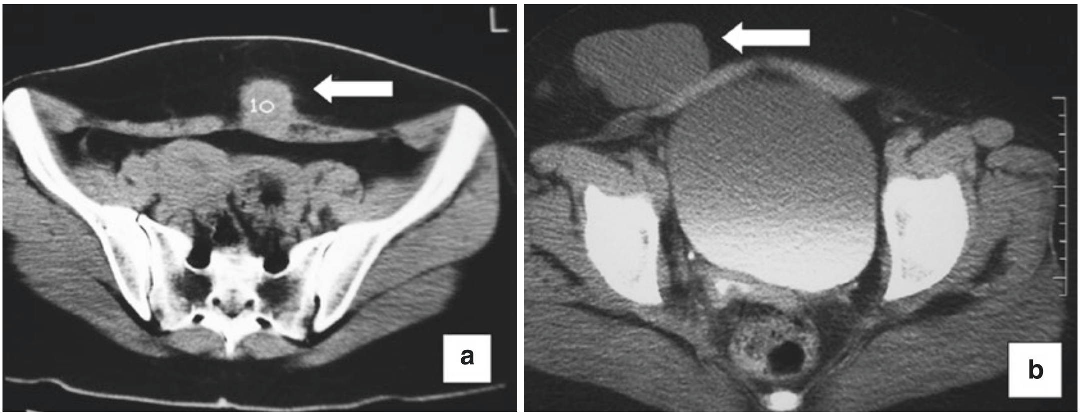

Fig. 5.31 CT images of masses in anterior abdominal wall, (**a**) in a vertical, and (**b**) in a Pfannenstiel incision (*arrows*). Reproduced with permission from [136]

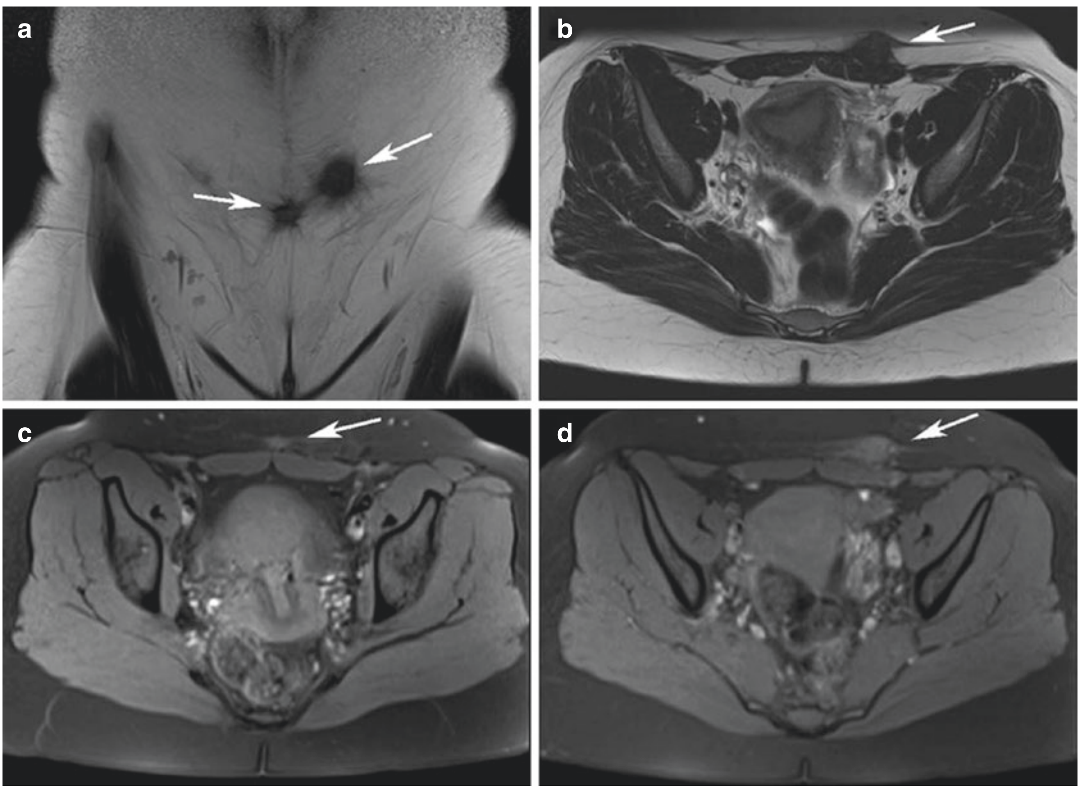

Fig. 5.32 Abdominal wall endometrioma in a 28-year-old woman with a previous history of Cesarean section. (**a**) Coronal T2-weighted image shows two lesions, in the left corner of the surgery scar and more centrally; (**b**) axial T2-weighted image shows lesion ventrally from the rectus abdominis; (**c**, **d**) axial T1-weighted images show slightly high intensity of AWE lesions compared with muscle. Reproduced with permission from [137]

intravenous contrast [134]. Due to its very high spatial resolution, MRI enables very small lesions to be detected and can distinguish the hemorrhagic signal of endometriotic lesions (Fig. 5.32) [135]. These imaging studies may be obtained if the lesion is very large, if there is a concern for fascial involvement, or if the diagnosis is in doubt. These data may assist with surgical planning if an abdominal wall reconstruction is anticipated.

5.4.4 Treatment

5.4.4.1 General Considerations

The management of an incisional hernia without incarceration in pregnancy is mainly conservative [73, 109]. The uncertainty about wound integrity of anterior abdominal wall and uterus during vaginal birth in these patients with a previous CS has led most obstetricians to favor an elective CS as the safest mode of delivery [73]. Also, the consultation with the patient is important because bilateral tubal ligation can be offered to (multiparous) patients who do not wish to undergo any more psychosocial trauma of pregnancy in such circumstances.

5.4.4.2 Anesthetic and Perioperative Management

See Chap. 21.

5.4.4.3 Prevention and Treatment of Preterm Labor

See Chap. 23.

5.4.4.4 Open Repair

Despite advances in surgical technique and materials, adequate fascial closure is mandatory. The best method is mass closure using wide bites with the sutures sufficiently close together so as to comply with *Jenkin's rule* which declares the need for four times the length of material as the length of the wound [138]. *Smead-Jones mass closure* is the closure of all the layers of the abdominal wall (except the skin) as one structure. The layered closure is described as the separate closure of the individual components of the abdominal wall and is associated with a significantly higher dehiscence rate compared to mass closure (3.81% vs. 0.76%) [139]. If a hernia is large, different surgical techniques using mesh should be used. If an incisional hernia is operated before planned pregnancy, mesh closure is strongly recommended. If operating on a pregnant patient with a large abdominal wall hernia, consultation with an abdominal surgeon for proper abdominal wall closure is mandatory because every subsequent postoperative hernia has a higher incidence of recurrence. Prosthetic mesh tends to contract and harden and may seriously interfere with abdominal expansion in pregnancies. Therefore, Abrahamson and Gorman, in the largest study with open repair so far, on 27 pregnant patients, recommend that these hernias are probably best repaired by the *shoelace technique* [140]. Probably it is better to use nonabsorbable suture material due to increasing intra-abdominal pressure and suture line tension during the continuation of pregnancy. Little has been reported about the fate of the abdominal wall subjected to further pregnancies following repair of ventral hernias (see Sect. 5.5.5.2) [140, 141].

5.4.4.5 Component Separation Technique

Since its initial description by Ramirez [142], the *component separation technique* has proven to be effective for the treatment of those giant abdominal hernias in which prosthetic material utilization is not indicated (Fig. 5.33). It can be used in emergency and elective settings. The first step in standard component separation technique is a separation of the skin and subcutaneous tissue from the anterior rectus sheath and external oblique aponeurosis. The latter is incised 2 cm lateral to the semilunar line to allow for separation of the external oblique from the internal oblique in their avascular plane, thus, allowing the rectus abdominis complex to be brought medially and approximated with interrupted nonabsorbable suture. Redundant skin is excised and the incision approximated over two closed suction drains. The postoperative course in the only published case was unremarkable, and the patient was discharged on postoperative day 5 with an abdominal binder recommended for the first 4 weeks postoperatively [143]. Drains were removed on postoperative day 7. Follow-up at 1, 6, and 12 months has confirmed the absence of recurrence (Fig. 5.34). The role of the abdominal binder during the postoperative period after abdominal wall hernioplasty is not defined.

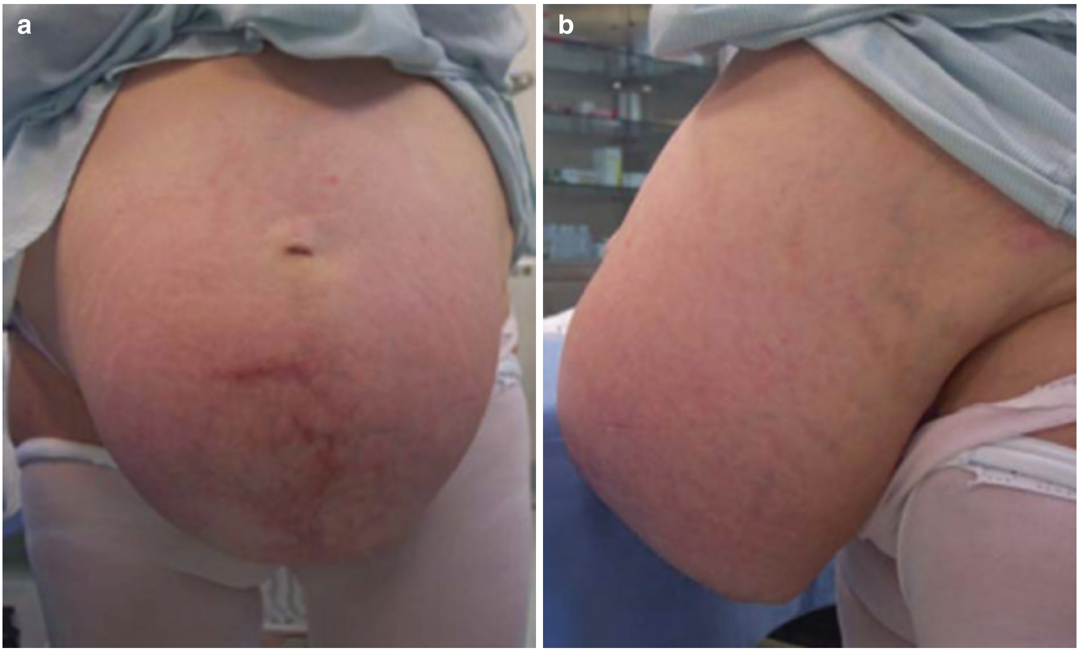

Fig. 5.33 Preoperative (**a**) frontal view and (**b**) lateral view of a 35-year-old woman after four vaginal deliveries. An incisional hernia was secondary to a laparotomy via an infraumbilical incision and right oophorectomy performed for ovarian cystadenoma. Reproduced with permission from [143]

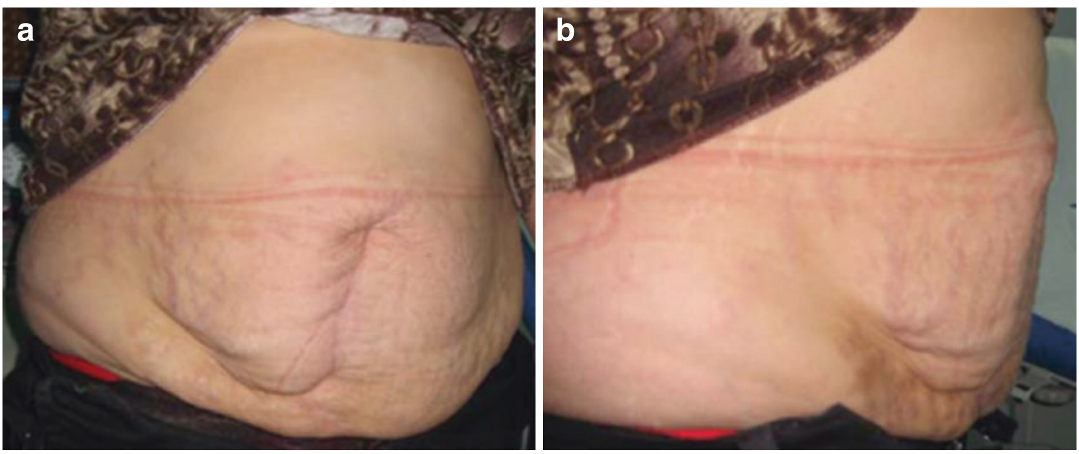

Fig. 5.34 Postoperative (after component separation technique) (**a**) frontal view and (**b**) lateral view (see text for details). Reproduced with permission from [143]

5.4.4.6 Laparoscopic Repair

Available data on treatment strategies for anterior abdominal wall hernias in women of childbearing age are scarce. No "best practice" guidelines exist. Data regarding laparoscopic repair in this patient category are nearly completely missing. There is only one case of laparoscopic hernia repair during pregnancy [144] and another with a successful vaginal delivery after previous laparoscopic repair of an omphalocele [145]. Schoenmaeckers et al. described a unique series of eight women who got pregnant and gave birth following laparoscopic repair of the ventral or an incisional hernia. Of those, four were incisional hernias [106].

5.4.4.7 Gravid Uterus

Complications

Potential complications apart from uterine incarceration or strangulation include spontaneous abortion, preterm labor, accidental hemorrhage, postpartum hemorrhage, intrauterine growth retardation, intrauterine fetal death, the complete evisceration of the gravid uterus [113], rupture of the lower uterine segment during labor [118, 120], or dysfunctional labor. Therefore, pregnant women and fetuses should be monitored closely.

Management

The management protocol for a pregnant patient with a large incisional hernia with the gravid uterus in a hernia depends upon the period of gestation. As the uterus remains a pelvic organ in the first trimester, there is no risk of incarceration during this period. In the second trimester, the pregnant uterus grows out of the pelvis and the risk of incarceration increases.

When it is diagnosed early and causes no symptoms, it can usually be managed conservatively until CS is performed at term. Conservative treatment with varying success includes manual reduction of hernia contents, rest, abdominal binders, and daily wound dressing with antiseptics if skin ulcerations are present [107, 109, 111]. A fetus is monitored with daily fetal movement counts, weekly CTG, and a repeated abdominal and fetal sonography every 3 weeks.

> ***Emergent operation*** during pregnancy is indicated when herniation of gravid uterus leads to incarceration, strangulation, burst abdomen, preterm labor, intrauterine growth retardation, accidental hemorrhage, intrauterine death, and rupture of the lower uterine segment [107, 109]. CS is recommended in cases with a previous CS or when fetal maturity is achieved.

Some recommend that hernioplasty should be performed after CS in the same operation [117], especially if decubital skin ulcers (Fig. 5.29) are present which necessitate surgical correction. Others claim that an incisional hernia during pregnancy is not an indication for CS per se [120]. It may not be feasible to perform lower segment CS in some patients due to unusual shape and contour of the uterus and an unapproachable lower segment; for these patients, a classic approach may be easier [111]. In addition, vaginal birth provides time for healing and a delayed repair to be scheduled. The management of emergent conditions depends on the gestational age at presentation. If strangulation of the uterus occurs at or near term, emergent laparotomy, CS, followed by immediate repair of a hernia is recommended. If the uterus is strangulated early in pregnancy, the immediate repair should be undertaken, and pregnancy is taken to term if fetal viability is present. Great care must be taken to avoid injuring any vital structures during incision of the abdomen, such as the small or large bowel, as it can be contained in the hernial sac, and the skin and peritoneum covering it may be very thin [120]. Additionally, enlarged uterus may make herniorrhaphy procedure difficult and unsustainable. Use of nonabsorbable mesh placed across an incisional hernia is routinely employed.

> ***Elective operation*** during pregnancy is indicated when (1) a hernia is so large that, despite conservative management, the uterus remains inside the hernia sac and is at increased risk of incarceration and (2) necrosis or ulceration of the overlying skin.

Because of the rarity of the condition, no consensus exists regarding the timing of the surgical repair or the ideal technique to be used. The authors have reported immediate and delayed repairs, with some favoring mesh repair and others opting for direct fascial closure [73, 113, 118, 120]. There are reports on the antenatal repair of an incisional hernia containing a strangulated uterus early in the pregnancy, followed by normal completion of gestation at term [108]. As this is obviously necessary for instances where

strangulation occurs early during gestation, an antenatal approach cannot be used in all patients because of the obvious operative and anesthetic risks associated with the surgery, as well as the potential detrimental effect that progression of pregnancy may have on the hernia repair [120]. When the ulcerated and redundant skin is present, it should be removed, the hernia ring excised, and the uterus returned into the abdominal cavity. Hernioplasty with mesh follows the same recommendations as for any other incisional hernia. In such cases perioperative antibiotic prophylaxis is mandatory.

5.4.4.8 Abdominal Wall Endometrioma

Medical management often results in temporary relief with the return of symptoms after the medication is discontinued. In addition, medications used during pregnancy could have harmful effects. The treatment of choice is wide local excision with negative margins [38, 44]. Wide excision, with at least a 1 cm margin, is considered the treatment of choice, even for recurrent lesions [130]. Abdominal wall endometrioma incorporated into the musculature requires en bloc resection of the underlying myofascial elements. Surgeons should be prepared for a coexisting hernia, and patients should be counseled that mesh repair may be necessary. Abdominoplasty and reconstruction with or without polypropylene mesh should be considered if a defect even without a hernia in the abdominal wall occurs, which may be caused by wide excision [146]. Procedures may be performed with local anesthesia, but unexpected surgical findings may call for a change of plan, and general anesthesia may be needed. Thus, these procedures should be performed in the operating room, and not in the clinic setting. All biopsy tracts should be excised [130, 147]. There are no data in general population to support postoperative hormonal therapy. However, this may be appropriate in patients with a history consistent with pelvic endometriosis [148] or in recurrent cases when a combination of surgical re-excision with hormonal therapy is also recommended [149]. There are no recommendations for combined therapy in the pregnant population.

5.4.5 Prognosis

5.4.5.1 Open Repair Before Pregnancy

Most surgeons are reluctant to repair ventral hernias for fear of being blamed for recurrence of a hernia after further pregnancies. Abrahamson and Gorman, with open repair before pregnancy, on 27 patients, recommend that these hernias are probably best repaired by the *shoelace technique* [140].

The operation is done under general anesthesia. The old scar is excised. The sac of a hernia and the rectus sheaths on each side are exposed. The new linea alba is constructed by suturing together two vertical strips 1–1.5 cm wide, each split off the medial edge of each anterior rectus sheath, using a continuous over-and-over suture of a monofilament polyamide loop. This suture line returns the unopened sac and its contents to the abdominal cavity and approximates the edges of the anterior rectus sheaths by bringing them together at the new linea alba. In larger hernias, a gap of varying width remains, with the continuous pliable to and fro shoelace suture adjusting itself to the differing widths and tensions across the fascial defect. The operation is entirely extraperitoneal and involves only two simple suture lines placed in normal healthy tissue; consequently, the postoperative recovery is smooth and rapid. In the usual shoelace repair where the patient has passed the childbearing age, the second suture, the shoelace, is pulled fairly tight under some tension in order to draw the flat muscles forward toward the midline. However, when young women intend to have further children, allowance must be made for the future distention of the abdominal wall with pregnancy by leaving the shoelace suture fairly loose, with no tension. This requires a much longer length of suture material which creates a good ratio between wound length and length of suture, and it is this that makes abdominal distention possible and with no recurrence of a hernia after pregnancies [138, 150]. The monofilament nonabsorbable synthetic polyamide suture is strong, extremely smooth, pliable, and inert and excites very little tissue reaction. These characteristics allow the suture to slide easily through the tissues and so adjust

Table 5.3 Baseline, operative, and follow-up characteristics of laparoscopic hernioplasty of an incisional hernia before pregnancy

Age	Children before LRIH	Children after LRIH	Mesh size	Fixation method	Months of LRIH after birth	Delivery	Abdominal wall pain in pregnancy	Recurrence
30	1	2	10 × 15 cm	DC	12.4	Cesarean	No	No
26	0	2	10 × 15 cm	DC	12.1	Vaginal	Yes	Yes
25	1	1	8 × 12 cm	T&TAS	44.4	Vaginal	Yes	No
24	0	1	10 × 15 cm	T&TAS	30.6	Vaginal	No	No

LRIH laparoscopic repair of an incisional hernia, *DC* "double crown" of tacks technique, *T&TAS* tacks and transabdominal sutures
Reproduced with permission from [106]

itself to the changing tensions and to the lengthening of the repair as the pregnancy progresses. Furthermore, the polyamide suture has the added advantage of excellent extensile strength, which confers on the material the ability to "give" or stretch with the changing tensions on the tissues and is, therefore, most suitable for the shoelace repair in young women who plan future pregnancies.

wall Although authors did not observe recurrences either during or after subsequent pregnancies or complications during pregnancies and deliveries, reservations regarding suture repair of even small hernias are well known, because of its very high long-term recurrence rate [151].

5.4.5.2 Mesh Repair Before Pregnancy

The foreign body reaction and scarring associated with mesh repair have in theory a potential to affect fertility and pregnancy. Given the expansion of the abdominal wall during pregnancy, biomaterial characteristics of shrinkage (more than 20%) and compliance should be considered. It has been previously shown that the flexibility of the abdominal wall may be restricted by large mesh implants [152, 153]. However, so far there are actually no data indicating that mesh repair of symptomatic ventral hernias should be prohibited in the reproductive woman who desires future pregnancy. In only other study of four patients with incisional hernias repaired before pregnancy (total of eight patients with epigastric, umbilical, and incisional hernias), one patient (25%) after laparoscopic mesh repair developed recurrence (Table 5.3). Other four patients (with two epigastric and two umbilical hernias) did not develop recurrence [106]. Of all operated patients, five women (63%) remembered a "tearing" or "pulling" pain at the area of the previous repair during the last months of pregnancy, of an intensity of 50 or more on a visual analog scale (scale 0 to 100). This pain disappeared immediately after delivery in all patients. All these six women who had given birth before and after LRVIH mentioned more pain in the abdominal wall during pregnancy after LRVIH than during pregnancy before LRVIH. None of the patients experienced chronic pain in the repaired area.

Available literature regarding pregnancy after mesh repair limited to a few case reports [145, 154, 155], and case series [106], indicates that pain is a significant problem associated with the mesh repair. This pain might occasionally require prolonged narcotic medications [154] or even intravenous "patient-controlled analgesia" [155]. The observation that more pain is present at pregnancy after LRVIH than at pregnancy before LRVIH clearly confirms the role of hernia repair in the genesis of this type of pain [106]. The development of pain after LRVIH might be caused by the fixation of the mesh [156] and the subsequent tension on this fixation during pregnancy. In one and only small series, the technique of mesh fixation (either double crown tack fixation or tacks and suture fixation) at LRVIH did not influence pain during pregnancy [106].

5.4.5.3 Abdominal Wall Endometrioma

The revealed recurrence rate in general population is 4.3% [45]. Therefore, adequate surgical

excision is essential to obtain a good outcome. No studies have addressed whether the size of surgical margin affects the recurrence rate. Follow-up evaluation is reported inconsistently in the literature.

5.5 Parastomal Hernia

5.5.1 Classification

5.5.1.1 Definition and Classification

A parastomal hernia is an incisional hernia related to an abdominal wall stoma [157].

Devlin classified parastomal hernias into four subtypes [158]:

- *Interstitial*, where the hernia sac lies within the layers of the abdominal wall
- *Subcutaneous*, where the sac of a hernia lies in the subcutaneous plane
- *Intrastomal*, where the sac penetrates into a spout ileostomy
- *Peristomal* (*prolapse*), where the sac is within a prolapsing stoma

No data are available to show differing complication rates, or increased incidence of symptoms, attributable to each of these different subtypes of a hernia. The classification system is, however, useful in enabling a specific comparison between different types of repair based on the subtype of a hernia. It also allows a specific description of any hernia detected by CT.

5.5.1.2 Ostomy Types

Three types of ostomies commonly seen in pregnant women include ileostomy, urostomy, and colostomy. The *ileostomy* (Fig. 5.35) is the most frequent. An ileostomy ɪs the surgical creation of an opening into the ileum on the abdominal wall for fecal diversion. The principal indication for ileostomy in younger population which includes pregnant patients is alimentary diversion due to ulcerative colitis and Crohn's disease. The *colostomy* is the least frequently performed for fecal diversion in young adults. A *urostomy* (ureterostomy), or urinary diversion, is an opening created in the abdominal wall that allows urine to pass directly out of the body. It is made in cases where long-term drainage of urine through the bladder and urethra is not possible (e.g., after extensive surgery or in the case of obstruction). In women of childbearing age, fecal or urinary diversion is related to inflammatory bowel disease, neoplasm, congenital anomalies, and trauma, malignancy, and polyposis syndromes [159]. The stoma may be located on the abdomen over the right, transverse, or left side. Some degree of paracolostomy herniation is considered to be an almost inevitable complication of colostomy formation, but complications are few and normal pregnancy, birth, and the postpartum period are expected [160].

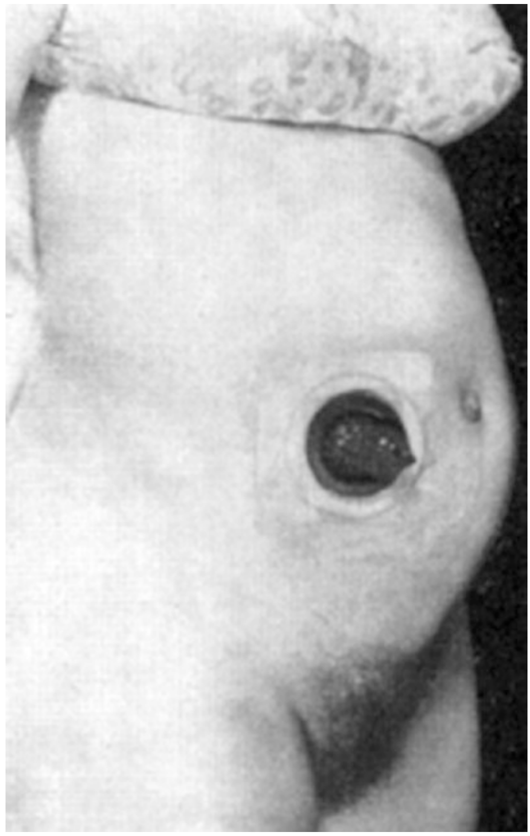

Fig. 5.35 Normally functioning ileostomy in late pregnancy. Reproduced with permission from [161]

5.5.2 Incidence

A parastomal hernia is an incisional hernia related to an abdominal wall stoma. A parastomal hernia affects 1.8–28.3% of end ileostomies and up to 6.2% of loop ileostomies in general population. Following colostomy formation, the rates are 4.0–48.1% and 0.3–31%, respectively [162]. Direct tissue repair or stoma relocation has recurrence rates of up to 50%, although the use of mesh lowers this considerably to 0–25% [163]. However, mesh placed in this onlay position around the stoma as a circumferential onlay can cause problems of erosion into the stoma or fistula formation in up to 5% of patients [164]. The prophylactic use of mesh prevents parastomal hernia formation by the placement of a lightweight sublay mesh at the time of stoma formation [165]. A possible explanation for the extremely rare incidence of incarcerated parastomal hernias in pregnancy is due to:

- Elective closure before planned conception
- Pregnancy as the relatively short period for the development of (clinically evident) a parastomal hernia
- Decreased possibility of incarceration due to the protective effect of enlarging uterus

Incidence in pregnancy is unknown, but due to increasing incidence of inflammatory bowel disease, probably more and more pregnant patients with stomas would be present and, therefore, increased incidence of (incarcerated) parastomal hernias.

5.5.3 Clinical Presentation

5.5.3.1 Medical History

There are no case reports dealing with incarcerated parastomal hernias in pregnancy. The presentation of a parastomal hernia with small or large bowel, especially incarcerated, is more complex in the pregnant population because nausea and vomiting affect up to 80% of normal pregnant women in developed countries [160]. Constipation is common in the third trimester and may also indicate a bowel obstruction of the pregnant ostomy patient. Intestinal obstruction is more likely to occur in mid to late pregnancy when the fetal head descends and immediately postpartum when there is an acute change in the uterus size [160].

5.5.3.2 Physical Examination

The examination involves removal of the appliance and inspection of the surrounding skin. The examination should be performed with the patient in standing and supine position performing a Valsalva maneuver [166]. A hernia appears as a bulge around the stoma. Digital examination of the stoma enables fascial aperture and parastomal tissue assessment.

Normally functioning stoma before pregnancy can enlarge and be at least 20 mm bigger (double) than it was prior to pregnancy.

This is the common situation and not the sign of ileostomy obstruction or (incarcerated) a parastomal hernia. If the stoma functions normally and the patient is without symptoms, the patient can be reassured and no diagnostic workup is necessary.

5.5.4 Diagnosis

If the history is suggestive of a hernia that cannot be demonstrated clinically, by plain abdominal X-ray or ultrasound, consideration should be given to abdominal CT scan which may detect subclinical hernias [167]. The diagnostic approach is the same as for other causes of obstruction. Prevention and management of fluid and electrolyte imbalances are a challenge for a pregnant woman with an obstructed ileostomy

who has lost the absorptive functions of the colon. Fluid and electrolyte substitution is necessary even if the patient is not vomiting due to intraluminal fluid accumulation. This is started at the beginning of the diagnostic workup.

5.5.5 Treatment

5.5.5.1 Conservative Treatment

Indications for emergent operation are the same as for other types of abdominal wall hernias in pregnancy – incarceration, strangulation, and/or perforation [168]. In the absence of emergency indications, conservative treatment is preferred in the form of rest, weight control, abdominal binders, and stool softeners [117]. Repair should be deferred until uterine involution postpartum to avoid the induction of collagen remodeling by relaxin during pregnancy [169], with the softened tissue predisposing to hernia recurrence.

5.5.5.2 Emergent Operation

Recognition and treatment of the obstruction require immediate relief of the obstruction, generally by nasogastric suction or surgical intervention. In cases of peristomal erythema and tenderness, the emergent operation is also indicated. If an obstruction with these skin changes is present, then a perforation of a bowel in a hernia should be suspected. Without obstruction, other diagnoses should be presumed as an abscess or necrosis from different primary diseases. The emergent operation is also indicated, but different surgical procedures are performed depending on the underlying cause. Cephalosporins (FDA category B) are introduced 30 min before incision and continued if indicated by intraoperative findings. In cases of incarcerated organ perforation (especially if contents are spilled into the free abdominal cavity) or obstruction of the large bowel, metronidazole (FDA category B) should be administered.

There are several techniques for the elective repair of different types of a hernia: open suture, open mesh, or laparoscopic mesh. In nonpregnant women, higher reoperation rate after inguinal hernia repair is not related to a particular technique. Consequently, routine use of open mesh methods in females is not recommended [170]. The situation is similar in an emergent situation. If the incarcerated content is the bowel, vitality is most important. Gangrenous bowel should be resected, and if Fallopian tubes and/or ovaries are necrotic, then resection (adnexectomy) should be performed. In these situations, hernioplasty with mesh is contraindicated because of a significant increase in the incidence of wound infections. Suture techniques are still widely used for the repair of umbilical hernias with a recurrence rate of 20% [65]. Thus, mesh repairs are performed more frequently with lower recurrence rates. There are no definitive conclusions in terms of technique, material, or mesh position. Surgical options for repair include peristomal hernia repair with or without mesh or stomal transposition with or without mesh repair. These operations could be done in open or laparoscopic fashion.

5.5.5.3 Anesthetic and Perioperative Management

See Chap. 21.

5.5.5.4 Prevention and Treatment of Preterm Labor

See Chap. 23.

5.6 Diastasis Recti Abdominis

5.6.1 Anatomy

The linea alba, the complex connective tissue which connects the left and right abdominal muscles, is particularly affected by the expansion of the abdomen [171]. The width of the linea alba is known as the inter-recti distance and normally varies along its length from the xiphoid to the pubic symphysis. In women between 20 and 45 years of age, the width of the normal linea alba is highly variable. The mean ultrasound width was 7 mm ± 5 mm (at xiphoid), 13 mm ± 7 mm (3 cm above umbilicus), and 8 mm ± 6 mm (2 cm below the umbilicus) [172]. Diastasis recti abdominis (DRA) is commonly diagnosed when the width exceeds these values.

5.6.2 Incidence

There is little research on this condition. Around 27% of women have a DRA in the second trimester and 66% in the third trimester of pregnancy. Around 53% of these continued to have a DRA immediately postpartum and 36% remained abnormally wide at 5–7 weeks postpartum [173]. The inter-recti distance decreases markedly from day 1 to 8 weeks and that without any intervention (e.g., exercise training or another physiotherapy), there is no further closure at the end of the first year [172]. In the urogynecological population, 52% of patients were found to have a DRA [174]; 66% of these women had at least one support-related pelvic floor dysfunction (stress urinary incontinence, fecal incontinence, and/or pelvic organ prolapse).

5.6.3 Classification

Clinically, it appears that there are two subgroups of postpartum women with DRA:

- Those who through a multimodal treatment program are able to restore optimal strategies for transferring loads through the abdominal canister with or without achieving closure of the DRA.
- Those who (A) in spite of apparently being able to restore optimal function of the deep muscles (optimal neural system) and who (B) do not have loss of articular integrity of the joints of the low back and/or pelvis (optimal articular system) and in whom (C) the inter-recti distance remains greater than normal (nonoptimal myofascial system) fail to achieve optimal strategies for transferring loads through the abdominal canister. In multiple vertical loading tasks (single leg standing, squatting, walking, moving from sitting to standing, and climbing stairs), failed load transfer through the pelvic girdle and/or hip joint is consistently found.

5.6.4 Treatment

5.6.4.1 Conservative Treatment

Most patients either do not have symptoms except bulge on the anterior abdominal wall or symptoms disappear during the first year postpartum. In these situations exercise for the strengthening of the anterior abdominal wall is necessary.

5.6.4.2 Surgical Treatment

When should consideration be given for an elective surgical repair of a diastasis rectus abdominis? The current clinical hypothesis is that:

- The woman should be at least 1 year postpartum [172], and a proper multimodal program for restoration of effective load transfer through the lumbopelvis [175] has failed to restore optimal strategies for function and resolve lumbopelvic pain and/or UI.
- The inter-recti distance is greater than mean values, and the abdominal contents are easily palpated through the midline fascia.
- Multiple vertical loading tasks reveal failed load transfer through the lumbopelvis failure to control segmental and/or intrapelvic motion (SIJ/pubic symphysis) during single leg loading (Stork or One leg standing test) [176, 177] and failure to control segmental and/or intrapelvic motion (SIJ/pubic symphysis) during a squat or sit to stand task [175].
- The active straight leg raise test is positive [178], and the effort to lift the leg improves with both approximation of the pelvis anteriorly and an approximation of the lateral fascial edges of rectus abdominis.
- The articular system tests for the passive integrity of the joint of the low back and/or pelvis (mobility and stability) are normal.
- The neural system tests are normal. The individual is able to perform a co-contraction of transversus abdominis, multifidus, and the pelvic floor, yet this co-contraction does not control neutral zone motion of the joints of the lumbopelvic which demonstrated failed load transfer on loading [175].

The second subgroup of postpartum women (see Sect. 5.7.3) have often sustained significant damage to the midline fascial structures, and sufficient tension can no longer be generated through the abdominal wall for resolution of function. For this subgroup, a surgical abdominoplasty to repair the midline abdominal fascia (the linea alba) is warranted.

5.6.4.3 Anesthetic and Perioperative Management

See Chap. 21.

5.6.4.4 Prevention of Preterm Labor

See Chap. 23.

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6 Symptomatic Diaphragmatic Hernia

Abstract

A diaphragmatic hernia is a rare condition during pregnancy, but symptomatic form carries high maternal and especially fetal mortality. Nonspecific symptoms are commonly attributed to other diseases especially because clinicians are reluctant to use plain chest X-ray which is often diagnostic. Fortunately, the use of thoracic sonography and thoracic MRI adds to earlier and more accurate diagnosis. As many cases present immediately after labor, abdominal and/or thoracic CT can be performed and is also diagnostic. If the patient is symptomatic, treatment is surgical mostly at the time of presentation. A treatment algorithm is less straightforward for asymptomatic patients detected during pregnancy. Some recommend surgical treatment to prevent complications during labor when increased intra-abdominal pressure occurs, while others operate only when symptoms develop. Type of the delivery is also not solved completely. While some recommend Cesarean section with simultaneous diaphragmatic hernia repair, others claim that vaginal delivery is safe with laparoscopic diaphragmatic hernia repair at a later date.

6.1 Historical Perspective

A diaphragmatic hernia (DH) was described for the first time by Sennertus in 1541, while the first two deaths were described by Ambrose Paré in 1575, one deriving from a strangulated bowel [1, 2]. Ude and Rigler in 1929 have observed the risk factors such as multiple pregnancies, large ovarian cysts, marge myomas, and ascites with malignancy [3]. In 1834, French physician Rene Laennec suggested that the diagnosis of DH could easily be made by auscultation of the chest and that a laparotomy could be used to withdraw the intestine from the thorax. The first recorded attempt at reduction of a DH in general population by laparotomy was made by Naumann [4] in 1888 but was unsuccessful. A year later, O'Dwyer [5] reported an unsuccessful attempt of repairing a strangulated congenital DH (CDH). Others state that Riolfi performed the first successful repair in 1886. In 1905 Heidenhain [6] reported a successful operation performed in 1902 for CDH in a 9-year-old patient when he reduced a hernia and closed the diaphragmatic defect through a midline laparotomy incision.

One of the first descriptions of incarcerated DH during puerperium is by Müller in 1913 [7]. The first available report with operative treatment in pregnancy is that of Crump in 1911, who

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_6

successfully operated upon a woman with DH complicated at 3 months pregnancy [8].

6.2 Etiology

6.2.1 Acute Diaphragmatic Fatigue

Acute diaphragmatic fatigue has been experimentally shown to occur in normal healthy subjects and in patients with the chronic obstructive pulmonary disease by asking them to modify their pattern of breathing or to breathe against high inspiratory resistances. During the expulsive period of labor, women are asked periodically to make strong expulsive efforts and to sustain them isometrically for many seconds; this is likely to produce "natural" diaphragmatic fatigue. Pregnant patients were studied in the delivery room from the moment of the rupture of the amnion until delivery of the infant occurred. The development of diaphragmatic fatigue was assessed both by measuring the static maximal inspiratory pressure and by analyzing the electromyographic power spectrum of the diaphragm.

These findings demonstrate that (1) the diaphragm is active in the expulsive efforts during labor and (2) the tension developed and the time each contraction is maintained may lead to the development of diaphragmatic fatigue. Therefore, evidence suggests that acute diaphragmatic fatigue is a natural condition [9].

6.2.2 Diaphragmatic Eventration

Diaphragmatic eventration is defined as an elevation of a hemidiaphragm without defects in the continuity. The muscular insertions are normal, the normal orifices are sealed, and there is no interruption of the pleural or peritoneal layers [10]. It is due to a thin floppy attenuation of a portion of the diaphragm that allows the intra-abdominal viscera to push the diaphragm upward to encroach the lungs. As more than 50% of adult patients remain asymptomatic, this condition often goes undiagnosed. The other 25% of patients have only mild exertional dyspnea. There are cases of pregnant women with eventration of diaphragm who became symptomatic at the onset of labor [11]. After labor lung and diaphragm function return to normal [11].

6.2.3 Diaphragmatic Hernia

DH is a defect in the diaphragm (the muscle that separates the chest cavity from the abdominal cavity). DH has been classified by Astley Cooper into three categories [9]:

- *Congenital*, defects in the diaphragm arising from the faulty embryologic development
- *Acquired*, develop at points of anatomic weakness, e.g., at the esophageal hiatus, aortic, or caval openings
- *Traumatic*, rents in the diaphragm arising from direct or indirect trauma

During the period 1928–1953, there were 54 patients with DH in pregnancy reported in English literature [12–17] and up to 2011 around 80 cases [13, 18].

6.2.3.1 Congenital

CDH occurs when the diaphragm does not form completely, leaving a hole. If the defect is in the posterolateral aspect, it is called hernia of Bochdalek, and if it is in the presternal (parasternal) region, it is called hernia of Morgagni–Larrey [19]. Morgagni DH results from a small defect between the attachment of the diaphragm to xiphoid process and seventh costal cartilage—the muscle-free space called the Larrey space.

The incidence of asymptomatic Bochdalek's hernia in the adult population is at least 0.17%, with a female-to-male ratio of 3:1 [17]. Parasternal or Morgagni–Larrey hernias are very rare comprising 2.5–3% of all CDHs. Despite such a high incidence in general population, the number of pregnancies complicated by unrecognized CDH is extremely small. Despite claiming the prevalence in general population of 1/2000–1/5000 live births [20], less than 40 cases in pregnancy have been reported since 1928 [14–16].

The pathogenesis of CDH is not well understood with many cases caused by gene mutations indicating that CDH is etiologically heterogeneous [20]. Other causes are toxins (pesticides, nitrofen) which cause increased expression of vascular cell adhesion molecule [21], decreased expression of vascular endothelial growth factor [22], and downregulation of fibroblast growth factors 7 and 10 [23]. Hernia of Bochdalek is the most common type of CDH. The posterolateral defect occurs in the left hemidiaphragm in 80% of cases because the right diaphragmatic space is stronger and further protected from a sudden increase in abdominal pressure by the liver [24].

6.2.3.2 Traumatic

Penetrating Trauma

Traumatic diaphragmatic injuries occur frequently after penetrating thoracoabdominal trauma with a reported incidence of up to 19% [20, 25]. Penetrating knife wounds in the chest usually result in pneumothorax or hemothorax, the majority of which will resolve with the insertion of a chest drain without requiring a thoracotomy. Injuries on the left side of the chest wall below the nipple level (fifth intercostal space) are at risk of injuring the diaphragm, many of which will be asymptomatic and present from 2 weeks to 40 years after the original injury [24, 26]. Ideally, a follow-up chest X-ray should be performed some weeks after recovery from the original injury, since abnormalities are present in most (94%) cases [27].

Blunt Trauma

Diaphragmatic rupture after blunt trauma is less common, with an incidence of 5% [28]. About 88% of reported blunt diaphragmatic injuries were the result of motor vehicle accidents [29]. Blunt trauma increases intra-abdominal pressure. The compression of the abdominal contents causes a bursting force to act on the undersurface of the diaphragm, which results in a linear tear in the line of the fibers from the region of the left central tendon toward the esophageal ring, but rarely into intact abdominal viscera for its transmission [27]. The thoracic cage is rarely extensively damaged, and if any ribs are fractured, they are usually below the level of the eight; this fact is also consistent with the force acting from the abdomen, rather than the chest.

In the nonpregnant patients, 90% of these hernias occur on the left side, because the liver offers protection to the right side and the left hemidiaphragm is weaker [24]. In general population, victims of lateral impact motor vehicle collisions are more likely to experience a rupture of the diaphragm than victims of frontal collisions. Occupants exposed to left lateral impacts are at greatest risk. The side of diaphragmatic rupture correlates with the direction of impact. Deformation shear is a more plausible mechanism for diaphragmatic rupture after lateral impacts [30]. Because the diaphragm is in constant motion, spontaneous healing after injury is unlikely. Commonly there is no pneumothorax, hemopneumothorax, or subcutaneous emphysema, one of which is usually present in severe injuries to the upper chest. The DH becomes evident mostly in advanced pregnancy [31].

Strangulation of abdominal viscera in a preexisting congenital or traumatic diaphragmatic defect is more common than in spontaneous rupture of the diaphragm; 21 such cases have been reported during pregnancy (16 congenital, 4 acquired, 1 spontaneous) up to 2004 [32–34].

Iatrogenic

The third cause of traumatic DH is iatrogenic and usually develops from thoracoabdominal surgery, such as esophagogastric surgery for esophagus cancer, gastric cancer, achalasia [35], or extensive oncologic operations in the upper abdomen [36]. There are several mechanisms. The paraesophageal DH most likely resulted from a weakness in the diaphragm from the myotomy surgery [37, 38]. Widening of the esophageal hiatus in the diaphragm could have resulted/worsened from the short interval of myotomy-to-pregnancy, increased abdominal pressure from the enlarging uterus, hyperemesis, and increased progesterone levels. How pregnancy might affect the healing of a myotomy scar or how long to wait after, before it is safe to get pregnant, is unknown. Another mechanism is that an unnoticed tear occurred during the previous splenectomy or that the left leaflet was weakened by the hemorrhagic

surgical procedure [33]. Since this patient's surgery, repeated increases in intra-abdominal pressure (caused by coughing, sitting positions, constipation, and straining) likely enlarged the unnoticed tear or contributed to further stretching of the weakened diaphragm fibers, eventually resulting in a rent. Pregnancy provides additive factors of increased intra-abdominal pressure: nausea and vomiting until the 16th week and the enlarged pregnant uterus in the second trimester. With advancing pregnancy, as the uterus enlarges, it forces an increasing amount of abdominal content into the chest. All these factors may convert an occult defect to one that is symptomatic and increase the risk of twisting and torsion of herniated viscera.

Spontaneous Rupture During Labor

Spontaneous rupture of the diaphragm during normal vaginal labor is extremely rare. It could result from a sudden sharp rise in the intra-abdominal pressure during the second stage of labor, exacerbated by application of external pressure to the uterine fundus or the upper abdomen. Pathophysiologic mechanism is similar to spontaneous rupture during a cough, and sometimes these two conditions could not be differentiated as a cause of spontaneous rupture of the diaphragm. A cough has three different phases: (1) the inspiratory phase, (2) the compressive phase, and (3) the expulsive phase [39].

A sudden sharp rise in the intra-abdominal pressure during vaginal labor is similar to the first and second phase of cough process. The inspiratory phase of a cough starts with a deep inspiration resulting in increased lung volumes and increased elastic recoil pressure. During the compressive phase, the glottis is closed and the expiratory muscles start to contract. As a result, the intrathoracic pressure increases to generate high-velocity flows for the expulsive phase of a cough. With the expulsive phase, the glottis opens and the high-pressure gradient generates rapid airflow. Both inspiratory and expiratory muscles are actively involved in coughing, and extreme changes in intrapleural pressure occur due to active contraction of these muscles [40]. The fracture of ribs as a complication of excessive strain during a cough can be explained by either of two different theories. The first mechanism of rib fracture in a cough is similar to that of stress fractures [41]. When a force (muscle contraction) is applied to an object (a rib), the object is subjected to stress. The stress will cause deformation of the object. When the deformation exceeds the elastic limit of the object, it undergoes inelastic deformation. Repeated trauma, as in paroxysms of a cough, can produce inelastic deformation in the most vulnerable part of the ribs, the middle third. This will result initially in minor cracks of the ribs and later, as the trauma continues, in fractures. Fractures can occur in any rib, but the ones most commonly involved are the fifth to tenth ribs [41]. The second mechanism of rib fracture may be due to opposing muscle forces acting on the ribs. The diaphragm is mainly an inspiratory muscle. The costal part of the diaphragm is attached to the lower six ribs and their cartilage. The muscles of expiration are the chest wall muscles, which include the internal intercostals, the triangularis sterni, the serratus posterior, the quadratus lumborum, and the abdominal muscles (including the external and internal oblique, the rectus abdominis, and the diaphragm) [42]. The diaphragm also acts as an expiratory muscle during activities requiring high intrathoracic pressure like coughing, vomiting, and sneezing [40]. This expiratory activity of the diaphragm is related directly to the intrapleural pressure and follows the expiratory activity of the transversus abdominis muscle. It is speculated that the diaphragmatic contraction will help to stabilize the thoracic cavity during the expulsive phase of a cough. A fracture line starts from a point 4 cm from the costochondral junction of the fourth rib running obliquely caudal and laterally to the ninth rib in the midaxillary line [42]. This line falls on the muscular attachments of the external oblique and serratus anterior muscles. The opposing actions of these muscles on the same ribs can result in fractures. Simultaneous contraction of the shoulder girdle muscles, especially of the serratus anterior, also contributes to the rib fractures by pulling the ribs upward and laterally, while the abdominal muscles pull the ribs medially and downward [42].

The development of a hernia during pregnancy is multifactorial, relating to the mass effect

of the gravid uterus, smooth muscle relaxation, and softening of ligaments. Obstructive shock during labor could have been offset by the increase in the venous blood return to the heart due to the spontaneous contractions of the utero-placental circulation, to the catecholamine release in response to labor pain, to the autotransfusion from the contracted uterus, and to the release of the aortocaval compression occurring during labor or immediate postpartum period [43, 44]. All reported cases of "spontaneous" rupture in pregnancy are left-sided. There are only seven cases of spontaneous rupture during labor [33, 34, 45–49], all on the left side. Causes of short and excessive increase of intra-abdominal pressure such as coughing in patients at risk especially chronic obstructive pulmonary disease or vomiting could also cause a spontaneous rupture that could become evident during pregnancy and/or labor or even early postpartum [47]. Spontaneous rupture of the diaphragm associated with vaginal delivery can happen in a patient regardless of age, the obstetric history (primigravida or multigravida), or a history of a diaphragm hernia. Reported diaphragm defects range from 3 cm to a large unmeasured tear (the hiatus to the chest wall). Larger tears tend to be associated with mediastinal shift [45].

6.2.3.3 Hiatal Hernia

Hiatal hernias (HH) are herniations of parts of the abdominal contents through the esophageal hiatus of the diaphragm. HH are six times more common in pregnant patients than the other two types [19, 36] and occur in up to 18% of multipara and 5% of primipara women [17]. There are four types.

Type I (*sliding*), the most common type, is characterized by widening of the muscular hiatal aperture of the diaphragm, with laxity of the phrenoesophageal membrane, allowing some of the gastric cardia to herniate upward. A sliding HH is probably related to loss of elasticity of these ligaments caused by factors such as excessive contraction of the longitudinal esophageal muscles, increased abdominal pressure, genetic predisposition, and age-related degeneration.

Type II (*paraesophageal*) results from a localized defect in the phrenoesophageal membrane. The gastroesophageal junction remains fixed to the preaortic fascia and the arcuate ligament, and the gastric fundus forms the leading part of the herniation. Paraesophageal HH represents 5% of all HH [17]. This condition is rare before the fourth decade of life; however, the patients involved are generally 20 years older than those with a sliding HH, suggesting that this is an acquired disease, evolving over the years [50]. These are true hernias surrounded by a peritoneal sac, and when the defect is large, incarceration with obstruction gastric volvulus and strangulation may occur [14, 19, 51]:

Type III hernias are a mix of types I and II.

There is also a *type IV* that is also called *complex HH*.

In the period 1903–1951, there were 19 cases of HH complicating pregnancy published [52], while during 1928–2012, 38 cases were published in the English literature [18, 53, 54]. The median age was 28 years and 67% were multiparous [18].

6.3 Clinical Presentation

6.3.1 Hiatal

Rigler and Eneboe in 1935 have shown that the association of HH with pregnancy is common, but they were unable to demonstrate any correlation between gastric symptoms and the presence or absence of a hernia [17]. Women may be asymptomatic until pregnancy when further herniation is caused by increased stress on the diaphragm by repeated vomiting in the first half of the pregnancy, a rapidly enlarging uterus in the second trimester, and Valsalva maneuvers during labor. The symptomatic phase includes flatulent dyspepsia, postprandial substernal discomfort relieved with vomiting, reflex cardiac irregularities (tachycardia and arrhythmia), and dysphagia. Some form of nausea and vomiting normally occurs in up to 80% of pregnant women in the first trimester. Recurrent vomiting in the second or third trimester associated with epigastric pain, retching of blood-stained fluid which may proceed to frank hematemesis and melena, or respiratory symptoms should raise the suspicion of complicated DH. If the disorder is complicated by reflux

esophagitis, which is common, there may be intense "burning pain" behind the lower end of the sternum, which may radiate up to the neck. There may be slight dysphagia, and a gastric ulcer may develop near the cardia. Retching of blood-stained fluid may proceed to frank hematemesis and melena. Stricture may develop at the lower end of the esophagus. Porter Vinson was the first to note the association between vomiting in pregnancy, esophagitis, and stricture. Probably an HH was present during pregnancy [55]. With the progression of DH, potentially fatal complications could occur, such as obstruction, torsion, strangulation, or infarction of the herniated viscera [36]. Resolution of symptoms is rapid in the puerperium, and attempts to make a postpartum diagnosis may be unsuccessful because of the diminution in size of a hernia or even its disappearance.

In the elective presentation, the diagnosis of HH should be suspected if:

- Symptoms persist after 12 weeks of pregnancy.
- The symptoms occurs after the firsttrimester.

6.3.2 Posttraumatic

The emergent clinical presentation after trauma consists of a combination of the mechanical effect on the cardiorespiratory function by the displaced viscera and the pathological changes in the viscera themselves consequent upon their displacement. The clinical entity is readily divided into three phases (no first phase in CDH) [56]:

1. Immediately following trauma
2. Quiescent period
3. Associated with strangulation

1. The early symptoms and signs become confused owing to the multiplicity of injuries likely to be associated with this condition: pain in the left chest or left upper back [57], pain in the left upper quadrant of the abdomen, left shoulder tip pain, vomiting, and shortness of breath associated with shock [56]. Even minor trauma, in a patient with a predisposition, such as a heavy cough or difficult defecation, can cause DH [57]. An expanding mass in the chest may displace mediastinal structures with compression of the vena cava, and this may impair venous return producing hypotension [43]. Compression and displacement of the lung cause the striking collapse of the lungs (atelectasis) which leads to hypoxia and dyspnea [47]. There is usually diminished air entry to a varying degree at the affected base, and the percussion note may be impaired or unduly tympanic. Tenderness and rigidity are common in the left upper quadrant of the abdomen. The consistency of this picture has been demonstrated by all left-sided lesions. It is considered, therefore, that if the X-ray shows an appearance, suggesting elevation of the left leaf of the diaphragm above its normal position, particularly if there are a large gas bubble and fluid level in the erect position, in a patient involved in the type of accident mentioned, the findings are pathognomonic of the ruptured diaphragm. The sequence of events from this point varies considerably. The lesion may continue directly to strangulation with a false "quiescent" period of only a few hours or may pass into a true quiescent phase, which may last up to several years. If strangulation follows immediately on the trauma, this is characterized by intractable vomiting. The vomitus may be of a non-bile-stained material or in the form of repeated hematemesis or merely dry retching. Severe pain develops in the left chest, left upper quadrant of the abdomen, and left shoulder tip. The patient becomes profoundly shocked and rapidly moribund. The elevation of the diaphragm and the size of the gas bubble are likely to be greater with strangulation than in nonobstructed cases. Carter has reported that the aspiration of serosanguinous fluid from the chest, when none was present before, is strongly suggestive of strangulation. It is of vital importance to recognize the onset of strangulation because if gangrene occurs, the mortality, even with the operation, approaches 100%, instead of being negligible in the absence of obstruction [58].
2. It is more common for the lesion to pass into a "quiescent" phase with the response to treatment of shock. The improvement may be so

rapid that the medical attendant is completely hoodwinked only to be rudely awakened by the sudden onset of strangulation after hours, days, months, or years. If the quiescent phase is prolonged, there may be no symptoms or only vague symptoms, such as shortness of breath on exercise or in advanced pregnancy due to increased intra-abdominal pressure [59]; substernal discomfort after meals; vague upper abdominal discomfort, sometimes relieved by vomiting or attacks; or subacute intestinal obstruction. These symptoms may be insufficient to make the patient seek medical attention.

3. Strangulation is one of the most serious complications of the DH. The onset of strangulation occurs most commonly within 3 years of the injury and its onset is usually sudden. It may follow raised intra-abdominal pressure due to unwanted straining or in the later months of pregnancy spontaneously. In many cases, the existence of a traumatic hernia is unsuspected, and the history of a previous accident may not be volunteered. The presence of an intestinal obstruction is probably recognized, but in the absence of abdominal distension and with the bizarre pattern of upper abdominal, chest, and shoulder tip pain, conservative management may be continued too long. There are cases where the compression of the left gastric vessels by the intact esophageal ring appeared to play a major part in the causation of gangrene or more commonly gangrene is associated with "direct" DH when the opening is smaller. Rare cases have been reported with a normal X-ray immediately after admission, but in whom herniation and even strangulation occurred later. It is presumed in these circumstances that omentum or the spleen temporarily covered the opening, but raised intra-abdominal pressure later caused the herniation.

The presentation on the right side may be quite different from that on the left, in that bowel is rarely herniated into the chest unless the tear is large and consequently the risk of strangulation is minimal. The symptoms of cardiorespiratory dysfunction are more in evidence because of the gross displacement of the lung, the paradoxical movement of the viscera through the large opening, and the gross loss of function of the right half of the diaphragm.

The main complications include visceral obstruction [19, 33], spontaneous [34, 47] or thoracocentesis-induced [32, 60] visceral perforation, visceral strangulation with or without subsequent gangrene and perforation/rupture [61], maternal respiratory distress [47, 62, 63], tension pneumothorax [60], tension gastrothorax [64], and maternal death [65]. They are more frequent during the third-trimester delivery and in the early postpartum period.

If the intrathoracic perforation is present, it includes nonsolid organ such as stomach and small or large intestine. Clinical presentation depends on the underlying pathophysiology. If strangulation precedes perforation, acute and significant abdominal and thoracic pain is present with the development of fever and shock. If strangulation with ischemia is not the cause of perforation as in a patient with a perforated intrathoracic peptic gastric ulcer due to excessive use of pain killers due to the persistence of a pelvic pain after the delivery, symptomatology could be less pronounced in the early stages [53]. This patient presented with subacute onset (3–5 days) of a clinical syndrome characterized by severe epigastric pain, moderate but worsening dyspnea, and fever.

Gibson in 1929 stressed the following diagnostic symptoms of strangulated DH in general population [66] which could be applied to pregnant population:

- Diminished expansion of the chest
- Impairment of resonance
- Adventitious sounds
- Cardiac displacement
- Circulatory collapse
- Cyanosis and dyspnea
- Asymmetry of hypochondria

Sometimes patients can hear a gurgling sound from the stomach or intestine in the chest. Diminished breath sounds on the ipsilateral side are the most common physical finding. The absence of abdominal distension is present if the stomach alone, unaccompanied by the intestine, is being herniated through the rent in the diaphragm with the presence of bloody fluid

in the left chest. Sometimes if peristalsis exists, bowel sounds can be heard during chest auscultation.

It is important to maintain a high index of suspicion of traumatic DHs in patients presenting with dyspnea or bowel obstruction and a previous history of the chest or abdominal trauma. Diagnostic problems arise if there is a previous stab wound to the chest many years ago. Small scars can be hidden below breasts, in inframammary fold, etc. In such cases, clinician does not even suspect possible previous diaphragmatic injury [67].

6.3.3 Congenital

CDH occurs most commonly during periods of elevated intra-abdominal pressure. In pregnancy, this period is present during the third trimester, vaginal delivery (especially with prolongation of the second stage of labor), or early postpartum [15]. Clinical presentation is similar to the second or the third phase of posttraumatic DH or a combination of these two clinical phases. During vaginal delivery or early puerperium, common combination of abdominal and respiratory symptoms exists. The presentation is with persistent nausea, vomiting (gastric, bilious, or feculent), epigastric pain, inability to pass flatus or stool, if intestinal obstruction is complete and/or new-onset dyspnea with pleuritic-type chest pain with radiation to the shoulder tip and/or back, tachypnea, cyanosis, and pallor. Early in the course of the disease, before hollow viscus perforation, the patients are afebrile. This should raise the suspicion of DH. The interval between the onset of symptoms and surgery ranges 10–48 h [45, 68]. Sometimes these symptoms and signs are present before or during pregnancy but in less exaggerated form, and patients take them as normal side effects of pregnancy [69].

6.4 Differential Diagnosis

Mild symptoms of maternal DH can imitate hyperemesis gravidarum or achalasia [35]. Pregnancy can make the diagnosis of achalasia more difficult as the increased levels of progesterone relax the lower esophageal sphincter, decreasing its resting tone and alleviating some of the symptomatology [70]. The similar clinical presentation is of diaphragmatic eventration [11]. In the majority of cases, the diaphragm eventration is found on the left side, and the most common cause is phrenic nerve injury secondary to trauma, infiltration, or neoplastic or iatrogenic compression during surgery. Those of congenital origin are caused by a partial or total lack of muscles in the pleuroperitoneal membrane, associated with chromosomal abnormalities and prematurity [71]. Eventration of the diaphragm produces a weakening of its normal structure and a higher risk of rupture in situations with an increase in intra-abdominal pressure, as it occurs during pregnancy: repeated vomiting, a rapid increase in the uterine size during the second trimester, or the Valsalva maneuvers during labor [46, 61]. Clinical examination of diaphragmatic eventration reveals dullness on percussion and absent or decreased breath sounds over the lower chest on the involved side. On deep palpation, the inspiratory excursion of the abdomen is less on paralyzed side, but paradoxically, the lower rib cage shows greater excursion on the side of paralysis. The diaphragmatic muscle is thin and weak (with either reduced, paradoxical, or absent movement on fluoroscopy and ultrasonography). The absence of fever or a cough helps differentiate DH from pneumonia or pleurisy. Another similar clinical presentation mostly without abdominal symptoms is a pulmonary embolism. Mostly it is suspected after Cesarean section (CS) [59]. Spontaneous esophageal rupture during pregnancy is very rare and, when it does happen, tends to be associated with hyperemesis gravidarum in the first trimester [72–74]. Opioid analgesia could potentiate the possibility of rupture. It impairs lower esophageal sphincter relaxation within minutes after intravenous administration [74]. If not clinically evident, an infected pleural fluid with a high amylase content is consistent with that diagnosis. However, the appearance of the material aspirated has a feculent odor, and gram stain reveals polymicrobial flora (especially *E. coli*, *Enterococcus* spp., and anaerobes); intestinal rupture is very likely [60]. If abdominal distension with (feculent) vomiting dominates, intestinal

Table 6.1 Differential diagnosis of a diaphragmatic hernia during pregnancy

Hyperemesis gravidarum
Achalasia
Diaphragmatic eventration
Pulmonary embolism
Intestinal obstruction
Acute coronary syndrome
Pneumothorax
Pneumonia/empyema
Asthma
Pleurisy
Esophageal rupture

obstruction from any cause is one of the differential diagnoses (Table 6.1).

6.5 Diagnosis

Diagnosis on clinical grounds is often difficult. Dyspnea of pregnancy is common because of gravid uterus pushing diaphragm 4 cm cephalad and resulting in a decrease in functional residual capacity and total lung capacity. However, moderate to severe dyspnea needs to be evaluated. Back pain is a frequently encountered symptom in expectant mothers, increasing the possibility that the cause of a backache will not be diagnosed; the chance of diagnosis is even less in patients with impending diaphragmatic rupture when anesthesiologists meet the parturient at delivery.

6.5.1 Chest Radiography

6.5.1.1 Plain Chest X-ray

The key to diagnosis in an elective or emergent setting is a chest radiograph which may show elevated diaphragm, pleural effusion (Fig. 6.1), retrocardiac air in the bowel lumen, air–liquid levels with hollow viscus obstruction (Fig. 6.2), nasogastric tube in the herniated stomach above the diaphragm, or only mediastinal shift to the contralateral side due to compression (Fig. 6.3) [46, 75]. Sometimes the findings of right Morgagni, a hernia, could be misinterpreted as *Chilaiditi sign* (radiographic finding of the bowel interposed between the liver and right hemidiaphragm) which is treated conservatively. There is a general reluctance to use X-rays in the pregnant population, but the dose is small, and in a selected population with a clear indication, the consequences of not performing the X-ray may far outweigh this small risk. The results are either diagnostic or abnormal and suggestive of diaphragmatic rupture in 75–97% of cases [75].

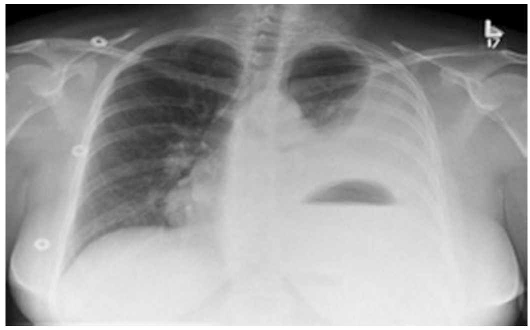

Fig. 6.1 Posteroanterior chest X-ray demonstrating a large left pleural effusion and gastric air–fluid level in the left hemithorax. Reproduced with permission from [61]

Fig. 6.2 Posteroanterior chest X-ray demonstrating colonic air–fluid levels in the left hemithorax. Reproduced with permission from [45]

6.5.1.2 Chest X-ray with Peroral Contrast

One should be cautious with interpretation because diaphragmatic eventration can look

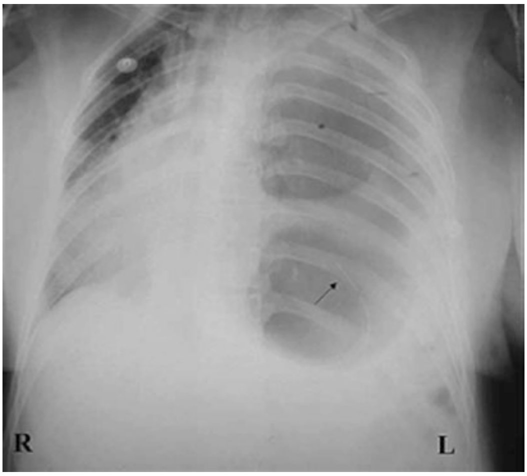

Fig. 6.3 Chest radiograph showing marked mediastinal shift to the right. In the left hemithorax are two large bullae. The *arrow* indicates the nasogastric tube in the herniated stomach above the diaphragm. Reproduced with permission from [46]

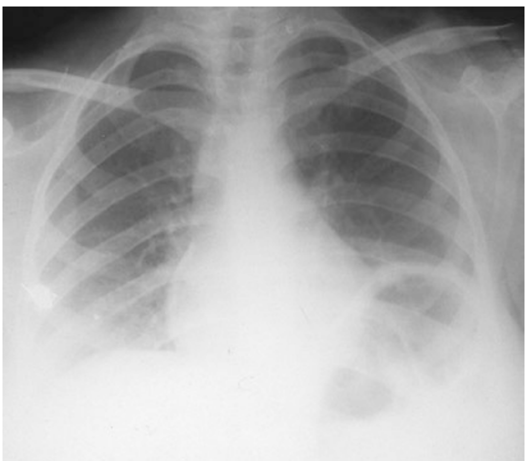

Fig. 6.4 The left dome of diaphragm is raised lying above the level of right dome with its peak reaching up to the seventh posterior rib suggesting eventration. Reproduced with permission from [11]

similar on chest X-ray which is not an indication for the operation (Figs. 6.4 and 6.5). If there is clinical suspicion without clear findings on plain chest X-ray, peroral barium contrast can help to establish the diagnosis with findings of contrast in various hollow organs located in the chest (Fig. 6.6). In addition, in the postpartum period, X-rays with contrast media can be used for the definition of suspected DH (Fig. 6.7).

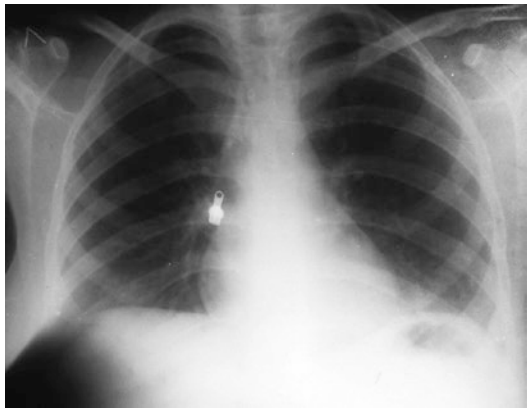

Fig. 6.5 Post-delivery chest radiograph of the same patient as in Fig. 6.4 showing resolution of eventration of diaphragm with normal position of the left dome at the left posterior eighth rib. Reproduced with permission from [11]

Fig. 6.6 Small bowel follow-through study to exclude an acute obstruction, with small bowel loops herniated in the left hemithorax. Reproduced with permission from [76]

With esophageal rupture, oral contrast usually reveals a defect in the esophagus.

6.5.2 Thoracic Ultrasound

Thoracic ultrasound may present valuable information about the integrity of the diaphragm, the content of eventration, and other diaphragmatic pathologies in general population [77]. There are no studies in pregnant population for the diagnosis of maternal diaphragmatic hernia.

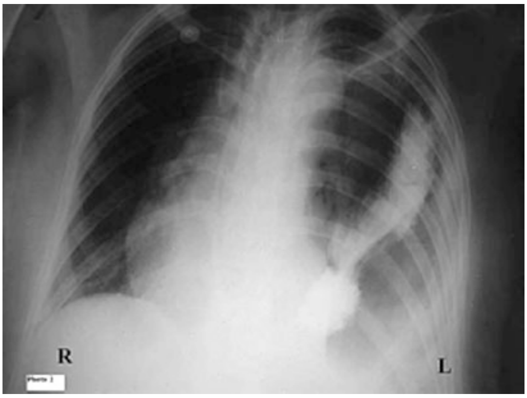

Fig. 6.7 Herniation of the stomach in the left hemithorax seen after Gastrografin ingestion in the postpartum. Reproduced with permission from [46]

6.5.3 Thoracic CT

If DH is suspected or proved, and the patient is stable, CT of the thorax and abdomen should be made. If the perforation is suspected, water-soluble peroral contrast should be used to detect the perforation and its localization. If the perforation is present, pleural effusion will be evident (Fig. 6.8). Also if partial obstruction/strangulation of the stomach is present, then the typical form of hourglass (the collar sign) is visible (Fig. 6.9). The stomach in the thoracic cavity causing a mediastinal shift is termed tension gastrothorax (Fig. 6.10).

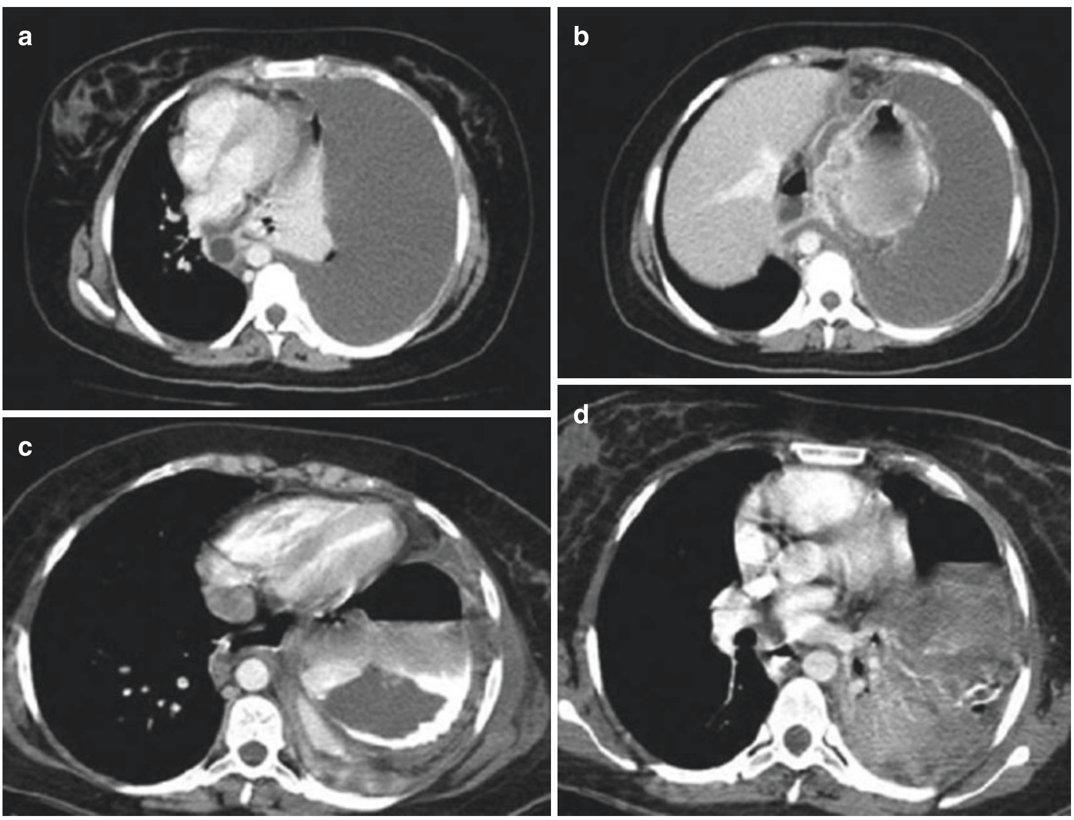

Fig. 6.8 First CT scan performed at admission shows (**a**) a massive left pleural effusion associated with severe contralateral mediastinal shift and (**b**) a complete intrathoracic gastric herniation. A second CT scan performed after chest tube placement and during water-soluble contrast examination demonstrates (**c**) the leak at the level of the stomach and (**d**) only a partial re-expansion of the pulmonary parenchyma. Reproduced with permission from [53]

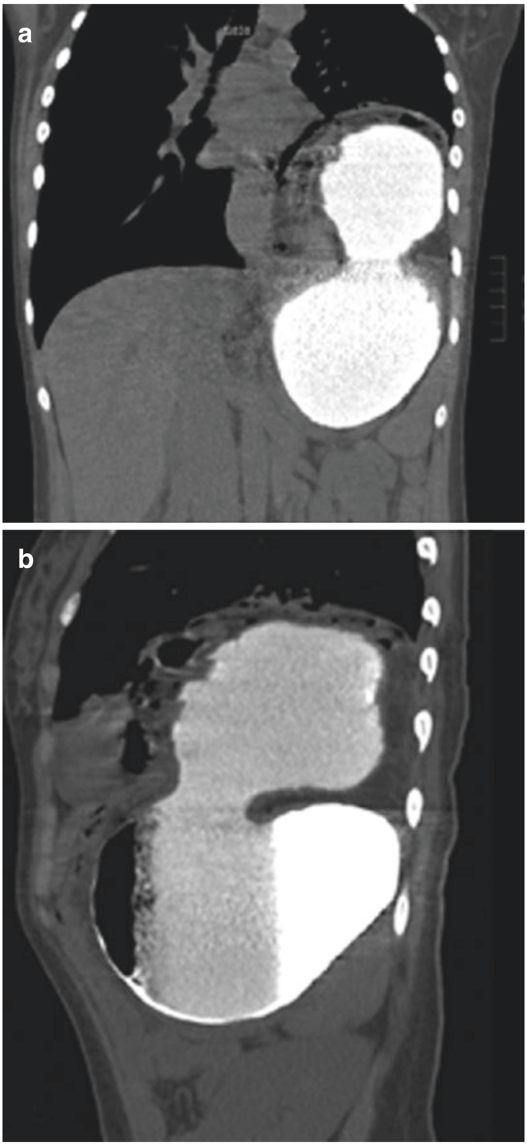

Fig. 6.9 Front view (**a**) and lateral view (**b**) of the CT scan showing the left diaphragmatic rupture and the typical aspect of the stomach, in form of hourglass (*the collar sign*). Reproduced with permission from [78]

6.5.4 Thoracic MRI

Recently, to eliminate the radiation exposure to both the mother and fetus, thoracic MRI, with high sensitivity and specificity [14, 79], has been used for the diagnosis (Fig. 6.11) instead of thoracic CT.

Fig. 6.10 CT scan of the thorax in the coronal plane in 21-week pregnancy. A mediastinal shift to the right (*black arrow*) with the left lung completely compressed (*white arrows*) by dilated stomach. *Intrathoracic stomach. Reproduced with permission from [64]

Fig. 6.11 MRI demonstrating Bochdalek's hernia with associated abdominal organs in the left chest. The *arrow* indicates the herniated portion of colon. Reproduced with permission from [14]

6.6 Treatment

In women of childbearing age with DH or eventration identified before pregnancy, consideration should be given to elective repair to prevent

diaphragmatic rupture and its associated risks during future pregnancies.

6.6.1 Conservative Treatment

In an emergent presentation during pregnancy, there is no indication for conservative therapy.

6.6.1.1 Nasogastric Suction

Treatment of nausea and vomiting by nasogastric suction in the form of preparation for the emergent operation is therapeutic because it decreases intra-abdominal, intragastric, and intrathoracic pressure. In addition, it lessens mediastinal shift if present improving oxygenation, especially when tension gastrothorax (herniation of the stomach with or without other intra-abdominal organs into the chest) is the cause [80]. Therefore it ameliorates symptoms, both gastrointestinal and respiratory [81]. Gastric decompression lowers intra-abdominal pressure and could improve the clinical condition of the pregnant patient with a DH who presents with symptoms and signs of obstruction. Such an improvement can allow surgery to be delayed until the patient is transferred to a tertiary care center or until antenatal corticosteroids are administered [14].

6.6.1.2 Oxygen

Oxygenation is impaired when abdominal organs are located intrathoracically. Therefore oxygen delivery in the perioperative period is mandatory.

6.6.1.3 Intravenous Fluids

Due to excessive vomiting and nil by mouth, dehydration with electrolyte abnormalities is present. The intravenous fluid administration should start immediately after the clinical examination.

6.6.2 Surgical Treatment

6.6.2.1 Operative Indications

Asymptomatic Patients

For asymptomatic patients, some recommend CS after fetal lung maturity with simultaneous hernia repair always before the onset of labor. The recommendation is based on the maternal and fetal morbidity being 55% and 27%, respectively, when vaginal delivery was attempted before the DH was repaired [19]. The fact that the majority of women who present have had previous uneventful pregnancies with the DH opens the question as to whether exposing an asymptomatic mother and fetus to the morbidity of antenatal repair is justified [18]. Up to 1935, only 12% of women with small and moderate degrees of paraesophageal DH during late pregnancy had the DH demonstrated radiologically in the postpartum period [17]. It seems, therefore, that though further stretching of the hiatus is possible during pregnancy and labor, the hernia will retrogress as soon as the abdominal tumor is removed, and in many cases, with only small and moderated degrees, the condition will revert to normal. This conclusion is supported by the cessation of symptoms in nearly all cases after the puerperium. Therefore, others [14] recommend *vaginal delivery* and the following:

- Planned induction of labor (to avoid precipitous labor at a remote site)
- Regional anesthesia to help prevent the urge to bear down
- The use of instrumentation to assist (shorten) the second stage

There are cases of symptomatic DH in previous pregnancies. Due to severe and prolonged vomiting and weight loss or even hematemesis, there are cases of fetal loss. In such cases, the elective repair should be undertaken to prevent similar presentations in further pregnancies [54].

Symptomatic Patients

Symptomatic DH should be managed without delay because of the associated high maternal and fetal mortality rates if left uncorrected [14, 19, 51]. Even if the pregnancy is normal, there is a possibility of puerperal symptomatology. One recommendation is that if the diagnosis is made in the first trimester, in the absence of complications, the patient should be carefully monitored and observed. Surgery is delayed until the second

trimester when organogenesis is complete before the increasing bulk of the gravid uterus risks further herniation. Others suggest repair shortly after diagnosis, regardless of gestation because the condition is associated with a poor or complicated outcome, particularly if early surgical intervention is not undertaken [19].

Emergent Presentation

A patient presenting with signs of visceral strangulation and infarction presents a surgical emergency, and immediate operation is indicated, irrespective of fetal maturity. This condition is associated with a high maternal and fetal mortality. If surgery (left thoracoabdominal or midline incision) demonstrates strangulation and gangrene of the herniated viscera, segmental resection of the involved portion of the large intestine with reestablishment of bowel continuity is indicated. The diaphragmatic defect should be closed with interrupted sutures. If the defect is large, the mesh should be used. The pregnancy is allowed to continue until 39 weeks of gestation, at which time elective CS is performed.

6.6.2.2 Anesthetic Management

See Chap. 21.

6.6.2.3 Perioperative Management

Pleural effusion or pneumothorax may be mimicked by the intrathoracic location of abdominal organs, leading to inappropriate thoracocentesis or tube thoracostomy and inadvertent perforation of the herniated viscera [60]. Gastric and/or biliary contents or intestinal or fecal smell confirms the diagnosis of (incarcerated) DH with abdominal organs in the hernia sac.

> Chest drains in pregnancy should always be inserted using blunt dissection [82].

The same surgical problem arises when a patient on admission presents as comatose, pale, and cyanosed. The blood pressure could be unrecordable and there are signs of a tension pneumothorax. It is true emergency, and a surgeon performs needle thoracocentesis inserted via the second left intercostal space anteriorly or standard tube thoracostomy. There should not be any problems with tube thoracostomy using blunt dissection. See Chap. 23 for details of other perioperative management recommendations.

6.6.2.4 Obstetric Management

The indication for the delivery and mode of delivery is trimester dependent. If a hernia manifests in the third trimester, once fetal maturity is documented, the baby should be delivered by CS with simultaneous repair of a hernia [18, 19, 46]. Standard vaginal delivery should be avoided because the increase in intra-abdominal pressure may further displace the viscera and result in strangulation of the herniated viscus or disruption of DH repair. On the contrary, others state that uterine contractions, unlike the Valsalva maneuver, do not increase the intra-abdominal pressure and are unlikely to cause rupture at the repaired site. Thus, a patient with a repaired DH can labor and deliver vaginally [14]. Unfortunately, it is impossible that labor can be completed without contractions of abdominal wall musculature and probably the Valsalva maneuver; therefore, it is safer to perform CS. Corticosteroids for fetal maturity should be administered to the mother before surgery if the gestational age is between 24 and 34 weeks because of the risk of preterm delivery during or after surgery. The patients who had undergone repair of a hernia during their first or second trimester can be allowed to deliver vaginally. Uterine contractions do not increase intra-abdominal pressure and are unlikely to cause rupture at repair site [14].

6.6.2.5 Open Surgery

Transthoracic Approach

Under normal circumstances, the best surgical approach is lateral thoracotomy, at the level of the seventh or eighth rib [45] because it provides a better view of the diaphragm, while it requires one-lung ventilation. If strangulation has occurred, the incision should be planned as a thoracoabdominal one for an adequate exposure and for easier access to the bowel, particularly if the colon is involved or a separate laparotomy incision. Even though this condition has been suc-

cessfully managed through an abdominal incision in the past, authors are now almost unanimous in advocating an eight rib transthoracic approach. The repair of the diaphragm, once the adhesions are separated, is easily achieved, and there is usually sufficient tissue to make a Mayo-type repair. If the tear destroys the musculature of the esophageal hiatus, this should be carefully reconstituted. When the diaphragm is avulsed from the chest wall and there is insufficient tissue left peripherally, repair should be affected by suturing the free edge to the chest wall with interrupted sutures to two adjacent intercostal muscles to obtain a wider adherence.

One opinion is that there is no justification for paralyzing the phrenic nerve, even by "temporary" crushing, but on rare occasions, it may be necessary to resect lengths of the lower ribs subperiosteally to allow closure of a peripheral tear. The thoracic cavity should always be drained by an underwater seal system. In the case of peptic intrathoracic perforation (Fig. 6.12a) due to NSAIDS, a gastric ulcer could be found (Fig. 6.12b). A primary repair with a double-layer suture of the gastric mucosa should be performed; then, after having replaced the stomach in the abdominal cavity, a direct double-layer closure of the diaphragmatic hiatal defect is completed.

Transabdominal Approach

The transabdominal approach enables good access to herniated parenchymal organs such as the liver and spleen [83] when mobile cecum is present and should be fixed or for anterior (Morgagni) DH (Fig. 6.13). Currently, the transabdominal approach is preferred because it is less

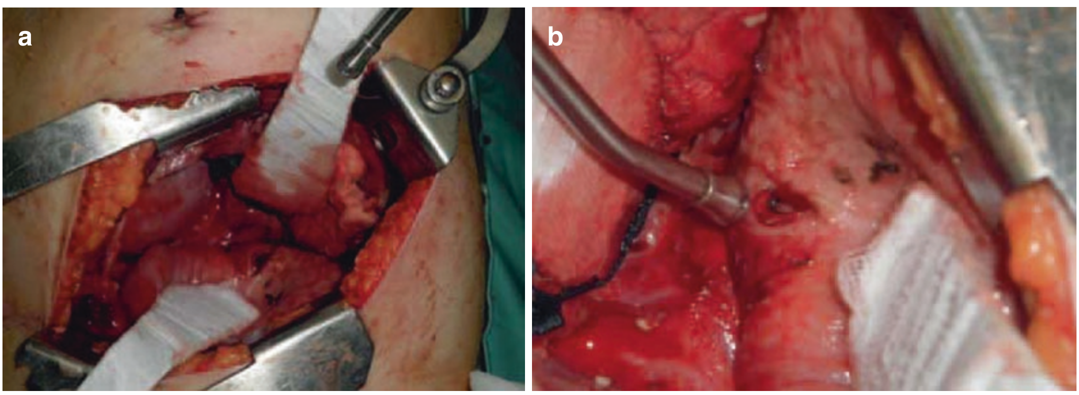

Fig. 6.12 Surgical findings during emergency thoracotomy: (**a**) complete intrathoracic gastric herniation through a large diaphragmatic hiatal defect without macroscopic signs of visceral strangulation, (**b**) a well-defined gastric ulcer (1 cm in diameter) at the level of lesser curvature. Reproduced with permission from [53]

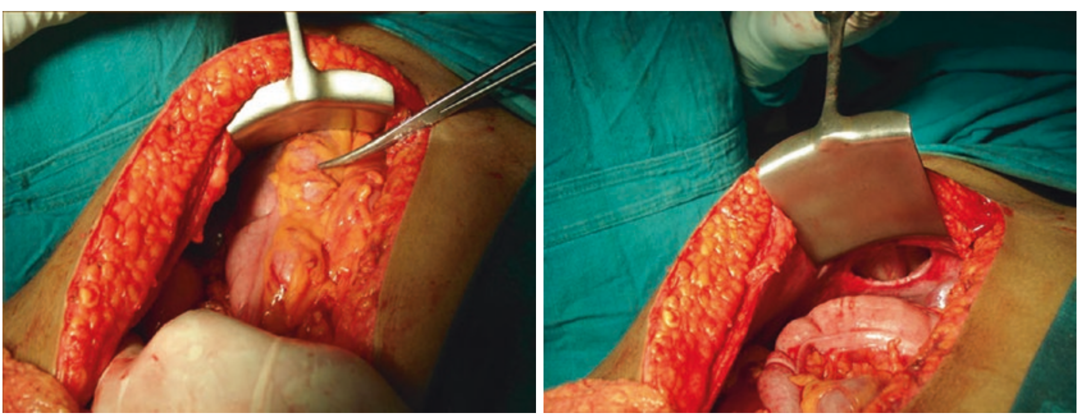

Fig. 6.13 (**a**) Herniation of the vital transverse colon and omentum through (**b**) anterior (Morgagni) diaphragmatic defect (6 × 4 cm), about 5 cm from the midline. Reproduced with permission from [85]

invasive for the patient [84]. However, some prefer the transthoracic approach in longer-lasting hernias to treat pleuroperitoneal adhesions. On the other hand, the transabdominal approach is better in pregnancy if CS is indicated or other intra-abdominal pathologic findings are present (gallbladder stones) which can be performed through the same laparotomy.

Thoracoabdominal Approach

The extended approach is when the abdominal incision is extended into thoracotomy or vice versa. The abdominal incision is necessary if wide resections of gangrenous organs are needed (Fig. 6.14).

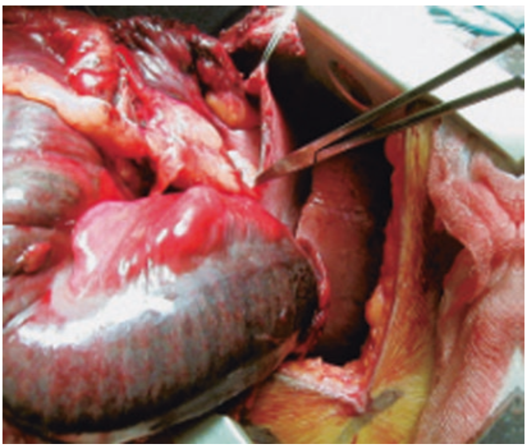

Fig. 6.14 Bochdalek's hernia in the left hemidiaphragm with the gangrene of a large part of the herniated transverse colon. Reproduced from [16] under the CC BY 4.0

6.6.2.6 Laparoscopic Surgery

Laparoscopic repair of DHs in general population was first reported by Campos and Sipes in 1991 [86]. It is now considered safe, feasible, and efficacious in nonpregnant patients [87]. However, in pregnant women, some technical difficulties might discourage surgeons from using this approach. Recently, more and more laparoscopic repairs during pregnancy are performed [62, 76, 88–93]. The disadvantage of laparoscopic access is that CS cannot be performed, but, on the other hand, laparoscopy can eliminate the need for extended laparotomy or thoracotomy. After the laparoscopic procedure, the classic incision for CS can be done with the addition of excellent cosmetic result. The pure laparoscopic operation can be done in the puerperium after vaginal delivery [62, 93] or CS [94].

Lateral Position

There is only one case of laparoscopic repair of a diaphragmatic hernia during pregnancy in the lateral position [76]. The lateral laparoscopic approach in diaphragmatic hernia repair has been already described in nonpregnant patients.

The patient is positioned in frank right lateral decubitus with double-lumen endotracheal intubation. An electronic fetal monitoring device is positioned on the right lower part of the abdomen (Fig. 6.15). An initial 12 mm port is inserted using an open technique, 2 cm below the left costal margin on the anterior axillary line. The pneumoperitoneum pressure is limited to 12 mmHg during the procedure. Three 5 mm ports and

Fig. 6.15 Frank right lateral decubitus was used with fetal monitoring during left diaphragmatic hernia (Bochdalek type) laparoscopic repair. Reproduced with permission from [76]

another 12 mm port are inserted under direct vision below the left costal margin. A10 mm 30 degree laparoscope is used. The DH with hernia contents is identified. The contents are reduced using gravity and atraumatic graspers and inspected for viability. Adhesions, if any, between the omentum and the left lower lobe of the lung are dissected with a monopolar cautery hook. The posterior and lateral chest wall insertions of the diaphragm could be mobilized to facilitate the approximation of the lateral borders of the diaphragm.

This position has many advantages over the more traditional supine position. First, it permits a complete view of the diaphragm, the subdiaphragmatic space, and the thorax. In this position, gravity helps to retract the spleen, the stomach, and the uterus without any manipulation. This reduces the risk of iatrogenic injury, especially to the gravid uterus. Also, if needed, a thoracoscopy could be easily accomplished without any repositioning. Right lateral tilt is usually discouraged during pregnancy because of the risk of inferior vena cava compression. Therefore, a more pronounced frank right lateral decubitus reduces the risk of inferior vena cava compression by a posterolateral displacement of the uterus. This position could be tried preoperatively with fetal and maternal monitoring (for 1 h), to ensure maternal hemodynamic stability and fetal well-being [76].

6.6.2.7 Diaphragmatic Defect Closure

The best method of closure of the diaphragmatic defect in the general population is still unclear. Primary repair is done for most defects unless they are very large (Fig. 6.16a). When the edges can be easily opposed, primary closure with non-absorbable sutures is certainly the preferred method. If the defect is large and difficult to suture, a prosthetic patch is recommended (Fig. 6.16b).

Some authors use Marlex mesh to close wide diaphragmatic holes and then cover the defect with a pedunculated flap, using the falciform ligament or the peritoneum. Gore-Tex mesh covered by the falciform ligament for closing a large diaphragmatic gap can also be used. The polytetrafluoroethylene patch is characterized by two different surfaces: one that promotes fibrous ingrowth into the patch and another that is relatively resistant to adhesion formation and placed adjacent to the abdominal viscera. Generally, a prosthetic patch should not be used if intestinal strangulation has occurred because of a risk of postoperative (mesh) infection. In clean-contaminated and contaminated conditions, wound and mesh-related infections occurred in 7–21% of patients in general population but did not usually require mesh excision [96]. Some authors advocate placing a prosthetic patch for abdominal wall reconstruction in clean-contaminated conditions [97]. The third option is

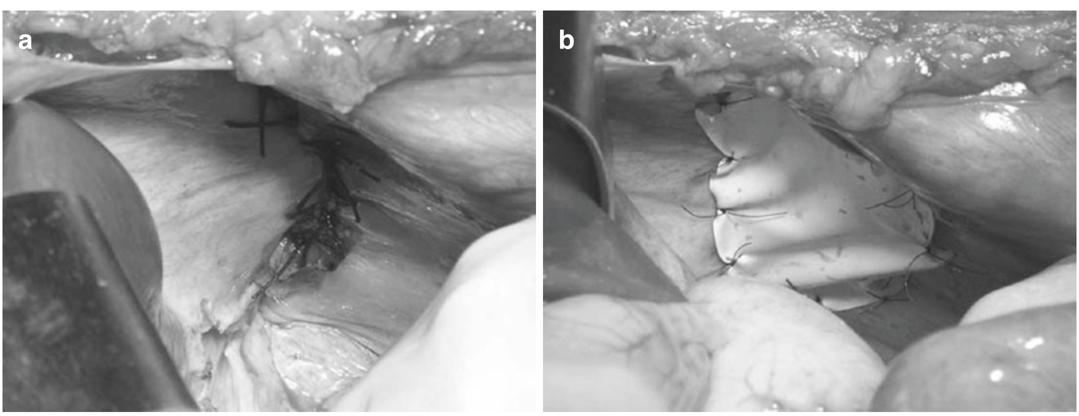

Fig. 6.16 (**a**) Completed hernia repair. A hernia was repaired with interrupted sutures. (**b**) Final appearance of the repair with the Gore-Tex sheet (Gore-Preclude dura substitute). Reproduced with permission from [95]

direct closure with sutures with the addition of a mesh [59].

There is extremely the small number of cases in pregnancy (less than 50), and specific indications for different procedures are not defined in pregnancy. Therefore, it is recommended to perform the procedure that is indicated in general population, especially in the subsets of patients with similar intra-abdominal pressure dynamics: (1) repair after CS in the same operation and (2) during the postpartum period.

6.6.2.8 Abdominal Organ Operations

Most principles are the same as in nonpregnant population. In addition, most principles are the same for pathologic conditions that occurred in the thorax instead of the peritoneal cavity. The question arises when obstruction or perforation of the ascending or transverse colon occurs. It can be caused by distension or strangulation or iatrogenic perforation with needle thoracocentesis or tube thoracostomy. Fecal spillage in the thorax does not cause peritonitis. It is not scientifically evaluated whether anastomosis of this segment can be performed in "native" peritoneal cavity without contamination [60].

6.7 Prognosis

6.7.1 Maternal Outcome

6.7.1.1 Maternal Mortality

Maternal mortality depends on the following:

- Type of presentation
- Type of DH
- Duration of symptoms
- Mediastinal shift
- Strangulation with/without perforation

The overall (symptomatic and incarcerated not separated as entities) mortality in the period 1916–1953 was 58.3% [65]. Currently, the mortality rate of chronic incarcerated DH can be as high as 20% whereas that of strangulated hernias may approach 85% [20]. The main life-threatening complications are acute respiratory distress caused by compression atelectasis, mediastinal shift, and strangulation and gangrene of the herniated viscera [19, 24, 33, 47, 62, 65]. In these cases, the maternal mortality rate ranges 42–58.3% [19, 34, 65, 98, 99].

6.7.1.2 Recurrent Diaphragmatic Hernia

The recurrence rate of DH following repair in general population depends on the severity of the original defect (ranging from minor to diaphragmatic agenesis) and the nature of the repair. About half of prosthetic patch repairs of CDHs showed evidence of re-herniation and required revision within 3 years [100]. This observation has two important issues. First, the prepregnancy repair is a risk factor for (recurrent) a diaphragmatic hernia during pregnancy, and also it is the risk factor for a recurrent diaphragmatic hernia after the repair during pregnancy, labor, or puerperium.

6.7.2 Fetal Outcome

Fetal mortality and morbidity result from premature labor and compromise maternal oxygen delivery [101]. Fetal deaths occur in 50% of cases, and premature birth has been reported in approximately 24% of cases [19]. In only 30% of the cases reported, delivery was by CS [18].

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Intestinal Obstruction

7

Abstract

Intestinal obstruction is one of five most common causes of nonobstetric acute abdominal conditions during pregnancy. A wide variety of causes can present during pregnancy as in the nonpregnant population. Some conditions are significantly more common in pregnancy than in the nonpregnant population. These include cecal and sigmoid volvulus and intussusception (when compared to the female population of the same age range) due to the growing uterus which displaces surrounding organs and increased intra-abdominal pressure. The presentation is similar or the same for any underlying cause of intestinal obstruction and depends on the level and severity of obstruction. Clinicians avoid to use plain abdominal X-ray which is commonly diagnostic and adds to earlier diagnosis which influences both maternal and fetal prognosis. Conservative therapy is rarely successful except for small bowel obstruction caused by adhesions but less successful than in general population due to partially fixed small bowel kinking by growing uterus. Other causes necessitate early surgical intervention to save both the mother and the fetus.

7.1 General Considerations

Women in a state of pregnancy may be purged, if there be any urgent necessity (or, if the humors be in a state of orgasm?), from the fourth to the seventh month, but less so in the latter case. In the first and last periods, it must be avoided.

Hippocrates

Let an abdominal scar on a pregnant woman be a line of evidence denoting potential obstruction.

Mathews and Mitchell

Intestinal obstruction in pregnancy is a consequence of a variety of etiological factors as in nonpregnant population. According to the cause of obstruction, there is a wide variety of therapeutic options available. Therefore, depending on the cause and the type, the duration, and of surgical intervention, the prognosis for the mother and the fetus is also variable.

7.1.1 Historical Perspective

The first published case of bowel obstruction in pregnancy was by Houston in 1841 [1]. Ludwig [2] in 1913 and Mikulicz-Radecki in 1926 suggested periods of increased incidence of obstruction during pregnancy. Ludwig in 1913 collected 95 cases. Ley-Klotz et al. found the tense band on the left flank of the gravid uterus causing mechanical obstruction with the cecum extremely distended and the rectum and sigmoid colon empty. A cecostomy was done, with recovery [3].

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_7

The first English language series was by Eliason and Erb in 1937 [4]. Two other major reviews included reports of 150 cases by Goldthorp in 1966 [5] and 64 cases by Perdue et al. published in the English literature from 1966 through 1991 [6].

7.1.2 Incidence

Incidence varies from 1/1500 to 1/66,431 [6]. Before 1940, when surgery was not so intensively performed, reported incidence was 1/66,431 deliveries [7]. In the next several decades, with more widespread use of surgery and decreasing postoperative mortality, the incidence increased from 1/12,000 deliveries to 1/3161 deliveries (Table 7.1). This large range is due to several reasons: (1) general failure to report this complication in the literature, (2) some cases are published in the journals that are not indexed in the most searched medical databases, and (3) over a century of publishing cases when surgical instruments and techniques evolved significantly but with varied use in developed and undeveloped countries.

Major causes of intestinal obstruction in the pregnant women include adhesions (mostly postoperative), volvulus, and intussusceptions [6, 8, 9]. Intra-abdominal adhesions are associated with 60–77% of intestinal obstruction in pregnancy [6, 8, 9]. Isolated small bowel obstruction has the incidence of 1/17,000 pregnancies [10]. Mathews and Mitchell's statement let an abdominal scar on a pregnant woman be a line of evidence denoting potential obstruction should always be remembered by obstetricians and surgeons alike. Intestinal volvulus is responsible for 25% of bowel obstructions in pregnant women but only 3–5% in nonpregnant patients [6, 8, 9]. Although incarcerated groin hernias are the second most common cause of intestinal obstruction in the general population, these cases account for less than 5% of obstructions during pregnancy [11] as well as intestinal intussusception [12–14].

Table 7.1 Incidence of intestinal obstruction during pregnancy in Queen Charlotte's Hospital and District, 1930–1964

Year	Rate
1930–1934	1/19,940
1935–1939	1/8919
1940–1944	1/12,214
1945–1949	1/18,445
1950–1954	1/3494
1955–1959	1/2888
1960–1964	1/3161

Reproduced with permission from [20]

Increasing incidence of bowel obstruction during the last century is due to:

- Older primiparas/multiparas
- Higher incidence of prepregnancy abdominal operations
- Decreased postoperative mortality
- World population growth

Probably the slowdown of increase of the incidence of adhesive obstruction will result from the more widespread use of laparoscopy. It is proven that laparoscopy reduces adhesion formation by 100% in the upper abdomen compared to laparotomy [15]. In the lower abdomen, the symptomatic adhesion formation was similar [16]. This should be differentiated from symptoms caused from adhesions—this is the only incidence of adhesion formation. There has been considerable controversy regarding the period in pregnancy when an obstruction is most likely to occur. Both Ludwig [2] in 1913 and Mikulicz-Radecki in 1926 suggested the periods of increased incidence:

- Fourth to fifth month when the uterus ascends from the pelvis
- Eighth to ninth month when the fetal head descends into the pelvis
- Delivery and early puerperium when rapid involution uterine size occurs

Some claim that most cases of intestinal obstruction in pregnancy present during the third trimester [17–19], and obstruction most commonly appears during the first pregnancy after surgery. Large bowel obstruction is less common than small bowel obstruction [6].

7.1.3 Clinical Presentation

The problem with intestinal obstruction is a large scale of severity of obstructive symptoms and signs which depend upon:

- Location of the obstruction
- The degree of obstruction
- The rate of progression of obstruction
- Intestinal perforation
- Underlying malignancy

The average duration from the onset of symptoms to hospital admission ranges 48–84 h. Once admitted, an average of 48–60 h passes before definitive surgery is performed. An average delay of 4 days continues to remain a significant contributing factor to the high morbidity and mortality observed in the pregnant population.

All colicky pain in pregnancy is not necessarily uterine in origin and, moreover, that premature labor can complicate intestinal obstruction and vice versa [21].

7.1.4 Differential Diagnosis

The most common differential diagnoses in pregnancy are discussed that are conservatively treated. In the sections with specific causes of obstruction, most common differential diagnoses are presented.

7.1.4.1 Constipation

Constipation is one of the most common medical conditions affecting the general population. Constipation is second only to nausea as the most common gastrointestinal complaint in pregnancy. Patients with no history of bowel problems may develop constipation for the first time during pregnancy, and, in addition, women who suffer from constipation prior to pregnancy will often find their symptoms are worse when pregnant. The prevalence of functional constipation, defined by the *Rome IV criteria* (Table 7.2), was 35%, 38–39%, 20–21%, and 17% in the first, second, third trimester, and the postpartum period, respectively [22, 23]. Others found that slightly fewer primiparous women (35%) suffered from constipation during pregnancy compared to multiparous women (39–42%) [24]. Symptoms of incomplete evacuation were the highest in the first trimester (21% decreasing to 12.5% in the puerperium) [25]. Overall, the sensation of incomplete evacuation and the time spent defecating were higher in all three trimesters of pregnancy than in the puerperium. Sensations of urgency decreased as pregnancy proceeded and leveled off in the third trimester. Urgency increased by 24% in the postpartum period compared with levels during gestation. There were no differences between lactating and nonlactating mothers. The causes of constipation in pregnancy are likely multifactorial including dietary factors, lifestyle issues, and hormonal and mechanical changes. Investigations are aimed at excluding treatable disorders such as hypothyroidism or hypercalcemia. A full blood count, thyroid-stimulating hormone (TSH), serum calcium, and glucose should be performed in all patients presenting with constipation.

Table 7.2 *Rome IV criteria* for the diagnosis of irritable bowel syndrome (criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis)

1.	Must include two or more of the following:
	Straining during at least 25% of defecations
	Lumpy or hard stools in at least 25% of defecations
	Sensation of incomplete evacuation for at least 25% of defecations
	Sensation of anorectal obstruction/blockage for at least 25% of defecations
	Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
	<3 defecations per week
2.	Loose stools are rarely present without the use of laxatives
3.	Insufficient criteria for irritable bowel syndrome

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The *Rome IV criteria* are a standard clinical measure of assessing chronic constipation but were not formulated with pregnancy-related constipation in mind (Table 7.2). Patients report symptoms relating to the frequency and difficulty in passage of stool that may not conform to strict diagnostic criteria. Patients may focus

Table 7.3 Laxatives in pregnancy

Safe	Caution	Unsafe
Lactulose	Saline osmotic laxatives	Anthraquinones (dantron)
Glycerin	Castor oil	Tegaserod
Polyethylene glycol (PEG)	Senna	
Bulking agents	Docusate sodium	

on symptoms such as straining, stools that are excessively hard, unproductive urges, and a feeling of incomplete evacuation. It is, therefore, possible that a patient may report constipation even when they have regular daily stools. A simplified set of criteria for the diagnosis of constipation includes low frequency of stools (<3 per week), hard stools, and/or difficulties on the evacuation of feces. These criteria are easier to use in routine clinical practice and are a good indicator of constipation in the pregnant woman.

As with any medication in pregnancy, laxatives should be used with caution (Table 7.3). Anthraquinone laxatives such as dantron are associated with congenital malformations [27]. Saline osmotic laxatives (magnesium citrate and sodium phosphate) can cause maternal sodium retention, while castor oil can initiate premature uterine contractions. Some laxatives can even produce neonatal diarrhea. Stimulant laxatives such as Senna should be used with caution in pregnancy because Senna can be excreted in breast milk [28]. In general, the short-term use of stimulant laxatives is considered safe in pregnancy. However, as with the general population, long-term use should be avoided.

> *The American Gastroenterology Association Position Statement* considers polyethylene glycol (PEG) to be low risk in pregnancy and the preferred treatment for chronic constipation in pregnant women [29].

PEG acts as an osmotic laxative by opposing the dehydration of bowel contents that would ordinarily lead to increased stool bulk. The increased retention of water in the colon lubricates and softens the stools. The small amounts (1–4%) that are absorbed are excreted unchanged in the urine. Lactulose, glycerin, and sorbitol are generally considered safe [29].

> Fiber-containing bulking agents such as Metamucil, Citrucel, and Perdiem are probably the safest laxatives to be used in pregnancy, as they are not systemically absorbed [29].

These agents take several days to exert their effects and are therefore not suitable for acute symptom relief. They are also contraindicated in fecal impaction. They can be used over long periods of time in patients with uncomplicated constipation. Adverse events related to bulking agents include excessive gas, cramps, and abdominal bloating.

7.1.4.2 Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional bowel disorder in the absence of any known abnormality of structure, affecting 9–12% of the general population. The *Rome IV criteria* define IBS as the presence of abdominal pain associated with a change in either the frequency or form of stool (Table 7.2). These symptoms must be present on at least three occasions per month over a 3-month period. When the patient has hard or difficult to pass stools greater than 25% of the time, with loose or watery stools less than 25% of the time, the diagnosis is constipation-predominant IBS (IBS-C). IBS is more common in females and is most frequently diagnosed between 30 and 45 years (i.e., the main reproductive years). It is therefore easy to see how constipation-predominant IBS can overlap with gestational constipation.

Tegaserod is a $5HT_4$ agonist that has shown considerable promise as a treatment for constipation-predominant IBS. AGA initially considered tegaserod to be low risk in pregnancy [29]. However, recent evidence of an increased incidence of ischemic cardiac and cerebral events in patients using this medication has led the Food and Drug Administration (FDA) to request that sale of tegaserod be suspended. Safe drugs used for idiopathic constipation can be used in constipation-predominant IBS.

7.1.4.3 Postpartum Acute Intestinal Pseudo-Obstruction

Incidence and Risk Factors
Ogilvie's syndrome (OS) was first described in 1948 [30] and is an acute colonic pseudo-obstruction without a mechanical cause. OS in pregnancy is rare and has been reported as isolated case reports or small case series. In 1976 of all published cases, 35% were after CS or vaginal delivery [31]. It has also been reported to occur after trauma, severe burns, abdominal and/or pelvic surgery, sepsis, electrolyte imbalance, spinal trauma/surgery, renal trauma/surgery/transplant, malignancy, congestive cardiac failure, and hip replacement and bed rest [32].

Pathophysiology
Current pathophysiology of OS is [33]: reflex motor inhibition through splanchnic afferents in response to noxious stimuli, excess sympathetic motor input to the gut (intestine does not contract), excess parasympathetic motor input to the gut (intestine does not relax), decreased parasympathetic motor input to the gut (intestine does not contract), excess stimulation of peripheral micro-opioid receptors by endogenous or exogenous opioids, and inhibition of nitric oxide release from inhibitory motoneurons. The mechanism of the condition is thought to involve loss of tone in the parasympathetic nerves S2–S4. This, in turn, results in an atonic distal colon and pseudo-obstruction. This explanation is given credence by the location of autonomic nerves close to structures at risk during CS, including the cervix and the vagina.

Various sources report a cut-off sign relating to an area of dilated and collapsed bowel around the splenic flexure corresponding to the transition zone between the vagal and sacral parasympathetic nerve supplies [32]. The cut-off sign is used to support the hypothesis of parasympathetic inhibition causing OS [32]. However, it is likely that the true pathogenesis is multifactorial. The association between OS and vaginal delivery may be due to the declining serum estrogen levels in the postpartum period [34]. In the case of OS following normal vaginal delivery, the histological findings of the cecum after right hemicolectomy showed no specific pathology [35].

Clinical Presentation
The diagnosis of OS in pregnancy and puerperium is widely reported to be troublesome due to the nonspecific clinical features [35]. The common clinical feature is significant abdominal distention [32]. Progressive abdominal distention is often painless at first. Importantly, bowel sounds are usually present and may be normal. Although patients may continue to pass small amounts of flatus or stool, the colonic function is generally inadequate. Abdominal pain, tenderness, and low-grade fevers are also common, while nausea and vomiting are rare [33]. Diagnosis should be kept in mind after CS when normal postoperative ileus is common but not prolonged and exaggerated as in OS [36].

Diagnosis
As with any case of suspected obstruction, electrolyte levels are an essential investigation, and 83% demonstrated at least one electrolyte disturbance with hypocalcemia being the most common [32]. Plain abdominal radiographs are generally diagnostic with significant colonic distention (cecal diameter ≥7 cm), with minimal or no distention of the small intestine [33]. Abdominal radiography is a standard first-line investigation, and a cecal diameter ≥9 cm (Fig. 7.1) is the "only definitive sign of imminent perforation" [35]. Serial plain abdominal X-ray is important for the definition of the progression along with WBC and CRP. CT can be used in doubtful cases to exclude other etiologies of obstruction (Fig. 7.2).

Conservative Treatment
Initial management should include intravenous fluid therapy and nasogastric suction. Patients should be fasting; if possible, all narcotic analgesics should be stopped. Colonoscopic decompression is successful in the majority of cases, unless signs of peritonism are evident, although recurrence is common [32]. Pharmacological treatment includes naloxone, cholinergic stimulation with neostigmine or

Fig. 7.1 Plain supine abdominal radiograph showing widespread colonic dilatation with no free air. Reproduced from [37] under the CC BY 3.0

Fig. 7.2 Abdominal CT showing widespread colonic dilatation with a cecal diameter of 8 cm. Reproduced from [37] under the CC BY 3.0

erythromycin, and cisapride, although the benefit in cases of idiopathic OS is not certain. Some support the use of laxatives in the postpartum period and stress the importance of early diagnosis [34]. The most important potential complication of the condition is large bowel perforation with subsequent fecal peritonitis and associated high mortality. Most cases of colonic perforation secondary to OS have been reported following CS [37, 38] but only two reports in the English literature after "normal" vaginal delivery [35]. One of these patients had third-degree tear during delivery, which required suturing in the operating room. The patient had been commenced on laxatives following the repair of the perineal tear and showed no symptoms of perineal sepsis. She presented with OS 5 days after vaginal delivery [39].

Surgical Treatment

Surgical treatment is indicated when:

- Cecal diameter >9 cm
- Progression of cecal distention or failure of resolution after several days
- Evidence of perforation
- Unsuccessful colonoscopy
- Recurrence after successful colonoscopy

Mostly, perforation occurs in the right colon and cecum according to Laplace's law. Perforation of the cecum is more common on the anterior tenia due to ischemia secondary to increased intraluminal pressure which prevents filling of the terminal anterior and posterior cecal arteries which anastomose on the antimesenteric surface. Surgical treatment comprises either cecostomy (preferred with appendectomy) or, if the ischemic bowel is present, limited right hemicolectomy with or without primary anastomosis (Fig. 7.3).

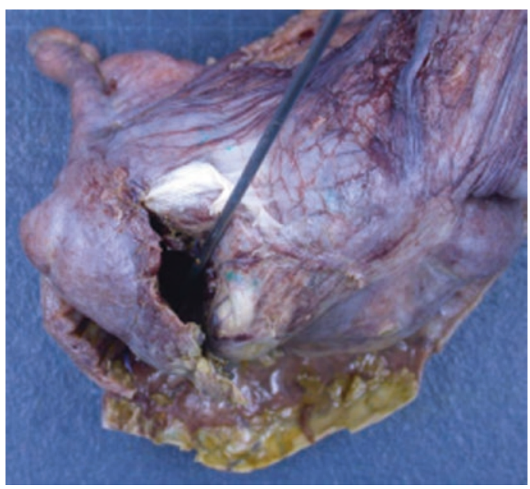

Fig. 7.3 The cecum with 4 × 4 cm perforation (no evidence of acute appendicitis or colitis) with surrounding exudate. Reproduced from [39] under the CC BY 2.0

7.1.5 Treatment

Conservative and surgical therapy for intestinal obstruction during pregnancy is discussed for every disease specifically throughout the chapter. One of the modalities of conservative strategy is presented here because if inadequately administered could cause many side effects.

7.1.5.1 Total Parenteral Nutrition and Refeeding Syndrome

Pathophysiology

Refeeding syndrome was first recognized during World War II when returning prisoners of the Japanese who had been starved rapidly developed neurological and cardiovascular abnormalities after the institution of a normal diet [40]. The pathophysiology of refeeding syndrome relates to the rapid rise in insulin production following a carbohydrate or protein shock when protein calories are administered at a rate above which the patient can tolerate. This can occur in those receiving even moderate dietary intake depending on their underlying nutritional, metabolic, or physical condition and may arise with the administration of glucose alone. This insulin release, associated with possible increased insulin sensitivity, leads to increased cellular uptake of glucose, fluid, and electrolytes with associated altered plasma availability of electrolytes.

Refeeding syndrome can manifest as either metabolic changes (hypokalemia, hypophosphatemia, hypomagnesemia, altered glucose metabolism, and fluid balance abnormalities) or physiological changes (i.e., arrhythmias, altered level of consciousness, seizures, cardiac or respiratory depression) and potentially death [41].

Total Parenteral Nutrition in Pregnancy

Total parenteral nutrition has been used successfully in pregnant women with hyperemesis gravidarum, postintestinal surgery, and acute pancreatitis [6]. In 1988, Levine and Esser reported that maternal and neonatal outcomes measured by adequate maternal weight gain and fetal growth were not compromised by total parenteral nutrition [42]. In pregnant women, the average daily intake through total parenteral nutrition should be 2430 kcal [43]. However, it is better to increase daily calories to avoid the refeeding syndrome.

Algorithms for initial management (Table 7.4) and for monitoring (Table 7.5) of refeeding syn-

Table 7.4 Initial management of refeeding syndrome

1. Identification and treatment of sepsis
• May not be clinically apparent but may explain an acute deterioration
• Low threshold for septic screen
• Low threshold for broad-spectrum antibiotics (orally or via NG tube if possible)
2. Fluid resuscitation and monitoring fluid balance
• Assess and carefully restore circulatory volume, monitor pulse rate, fluid intake, and output
• Malnourished patients have a reduced tolerance of intravenous fluids in moderate to high intakes (>2 L/24 h) that can lead to heart failure
• Administration of intravenous fluids may be necessary for the initial 72 h until sufficient oral intake is achieved
• If evidence of dehydration, for careful rehydration, i.e., 1–2 L in the first 24 h depending on response. Greater volumes only if severely dehydrated
• Total fluid intake (including intravenous, enteral, and oral) should aim for a maximum of 30 mL/kg/day (≤1.5 L)
• At least 6-hourly monitoring of blood pressure, pulse, and respiratory rate is necessary to detect evidence of heart failure or inadequate intravascular volume
3. Correction of electrolyte abnormalities
• Ensure recent (last 48 h) electrolyte levels are available. These should include: urea and electrolytes, phosphate, calcium, magnesium (add to standard blood profile), liver function tests, and full blood count
• If electrolytes are deranged, consider and treat possible causes
• Perform ECG if potassium is less than 3.5 mmol/L or phosphate is less than 0.80 mmol/L

(continued)

Table 7.4 (continued)

• Organize supplementation if phosphate <0.8 mmol/L, K <3.5 mmol/L, Mg <0.5 mmol/L, or adjusted Ca <2.0 mmol/L
• Caution should be used in renal patients due to the reduced excretion of these electrolytes
If very low plasma electrolyte values are demonstrated, e.g., phosphate <0.32 mmol/L
• K <2.5 mmol/L, Mg <0.5 mmol/L, then the institution of feeding or nutritional support may result in a further drop of these electrolytes to possibly critical levels. Electrolyte correction with oral or intravenous supplementation is required to achieve levels above these thresholds before the institution of feeding
4. Correction of hypoglycemia/blood sugar control
• Monitor blood glucose once to twice daily unless more frequent tests are indicated (i.e., for those patients with known diabetes or IGT)
• If hypoglycemic replace intravenous fluids with 5% glucose
5. Management of hypothermia
• Monitor body, and if necessary core, temperature at least daily
• Hypothermia is commonly associated with malnutrition. Its correction should be simultaneous with fluid rehydration and can include provision of heated drinks and blankets
6. Correction/prevention of micronutrient deficiencies
• Administer thiamine 100 mg orally or crushed via feeding tube three times daily for 10 days or until recommended feeding rate reached with the first dose being administered at least 30 min before instituting feeding
• If enteral route is not available, patient has anorexia nervosa or has chronic alcoholism; administer Pabrinex IVHP—one pair of ampoules 30 min before instituting feeding and then daily until recommended feeding rate reached
• Administer vitamin B compound strong (one tablet three times daily) and Sanatogen Gold (one tablet daily) orally or crushed via feeding tube

Table 7.5 Monitoring of patients with suspected or proven refeeding syndrome (minimum 72 h)

Monitor until levels in reference range or patient on stable feeding regimen
• Serum urea and electrolytes, adjusted calcium, phosphate, and liver function tests at least daily
• Serum magnesium; baseline, every 3 days and then weekly once stable
• Fluid balance daily
• Blood glucose once to twice daily unless more frequent tests are indicated
• Temperature, pulse, respiration, heart rate; daily
• Blood pressure 6 hourly
• ECG if abnormal heart rate or pulse. If evidence of cardiac abnormalities on assessment or during refeeding, patient will require cardiac monitoring. If necessary transfer to appropriate ward

drome from the *Drug Therapy Guideline No: 46.00 Issued: 10.10.07 Refeeding Syndrome Guideline (NHS trust)* are presented:

Clinical deterioration may reflect rapid overfeeding, too little is always safer than too much, half the rate of feeding and observe.

7.1.6 Prognosis

7.1.6.1 Maternal Outcome

In the past, maternal mortality from intestinal obstruction was significantly high, reaching 60% in 1900 [44]. Around 1937, maternal mortality was lowered to 21% [6]. Modern rates of maternal mortality have shown continued improvement, with reported incidence of 12% in 1966 [5, 20]. In recent series, maternal mortality decreased to 6%. Maternal mortality by etiology is found in specific sections of this chapter.

7.1.6.2 Fetal Outcome

Intestinal obstruction in the second trimester caused premature labor with subsequent neonatal death in 33% [45], whereas the perinatal loss in the third-trimester obstruction was 47% [46]. Neonatal mortality remains high, 20–26%, while around 1937 it was 50% [6]. Hypoxia and hypotension during anesthesia should be prevented as these significant factors for fetal death.

7.2 Intussusception

7.2.1 General Considerations

Intussusception was usually fatal until early twentieth century. John Hunter described the clinicopathological characteristics. Sir Fredrick Treves, an eminent nineteenth-century surgeon described the plan of treatment, which by and large remains valid to date [47]. Adult intussusception is rare and present in 1/30,000 of all hospital admissions, 1/1300 of all abdominal operations, 1/30–1/100 of all cases operated for intestinal obstruction, and one case of adult intussusception for every 20 childhood ones [48]. Mean age at presentation tends to be in the sixth decade of life [48, 49]. Higher age at intussusception may point to underlying malignancy since the mean age for benign cases is 44 years as opposed to 60 years for the malignant [49]. About 80–90% of intussusceptions in adults are secondary to an underlying pathology typically associated with tumors, granuloma formation, a foreign body, or an anatomic defect. Small bowel intussusceptions in adults are secondary to benign lesions in most cases, with malignant lesions causing 15% of cases and idiopathic intussusceptions accounting for approximately 10–20% [50]. The male-to-female ratio is 1:1–1.3 [51]. This entity can be classified into four distinct categories [49]:

- *Enteric*, in which the intussusception is confined to the small bowel
- *Ileocolic*, in which the ileum invaginates through a fixed ileocecal valve
- *Ileocecal*, in which the ileocecal valve itself is the lead point for the intussusception
- *Colocolic*, in which the lead point is restricted to the colon

It may be acute or chronic (persistent or intermittent) in addition to being "silent" [52]. The chronic intussusception may have lasted in some instances for a year before the diagnosis. Although in small bowel intussusception in adults surgical intervention is considered necessary when patients are symptomatic, many asymptomatic and likely transient intussusceptions may be incidentally detected on CT.

7.2.2 Historical Perspective

The first known cases of intussusception in pregnancy are the intussusception of the rectum described by Berthold Ernest Hadra (Fig. 7.4) in *The Richmond and Louisville Medical Journal* in 1876 and by Williamson in 1914 as the jejunal intussusception through gastroenterostomy after vaginal delivery of a stillbirth in the 34th week of

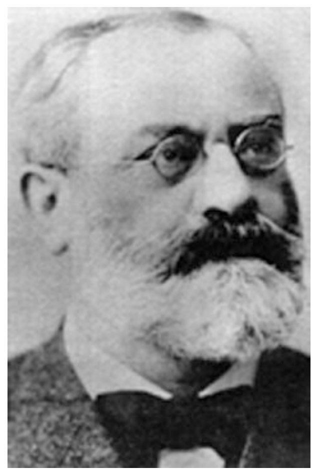

Fig. 7.4 Berthold Ernest Hadra (1842–1903), physician and surgeon, was born near Breslau, Prussia (now Wrocław, Poland). He obtained his medical education from the universities of Breslau and Berlin. He was appointed the chairman of Surgery at Texas Medical College at Galveston in 1888 and helped to transform that institution into what is now known as the University of Texas Medical Branch at Galveston. He received international respect for his pioneer work in the fields of surgery and gynecology (Courtesy of *American Association of Neurological Surgeons*, 2004) [54]

her second pregnancy. Before first pregnancy, she was twice operated due to peptic ulcer [53].

7.2.3 Incidence

7.2.3.1 Pregnancy

The incidence of intussusception is similar in pregnant and nonpregnant women [55]. Intussusception as a cause of intestinal obstruction found in 5–6% [6, 56] of pregnant patients with intestinal obstruction. The most common type of intussusception occurring in pregnancy or puerperium is ileocecal [55, 57, 58], and Meckel's diverticulum is the most common precipitating factor in pregnancy [59]. Chaffen, Mason, and Slemons, in 1937, collected 20 cases which were associated with pregnancy either before labor, at labor, or in puerperium [60]. In one study 30% (3/10) of intestinal obstructions during pregnancy were caused by intussusception [19]. There are only several cases of primary intussusception in pregnancy published. Probably this is due to the bimodal incidence of intussusception—in the childhood and with increasing incidence during life with the second peak in the sixth decade of life. Postoperative invaginations are also found, one of the first published by Williamson (see Sect. 7.2.2).

After LRYGB, 0.1–0.3% of the patients in general population will develop an intussusception [61], but the percentage after LRYGB during pregnancy is currently unknown.

7.2.3.2 Puerperium

Even an idiopathic intussusception in puerperium after normal vaginal delivery happens [62]. Another two cases of post-CS intussusception are published. One case is secondary to colonic adenocarcinoma and another of idiopathic intussusception of 27-year-old women with preeclampsia with ileoileal invagination 80 cm proximal to the ileocecal valve which was manually reduced [63].

7.2.4 Etiopathogenesis

Masses in the bowel or lumen act as an irritant and provoke abnormal peristaltic movement, which may lead to the telescoping of one bowel segment over the adjacent segment. Intussusception

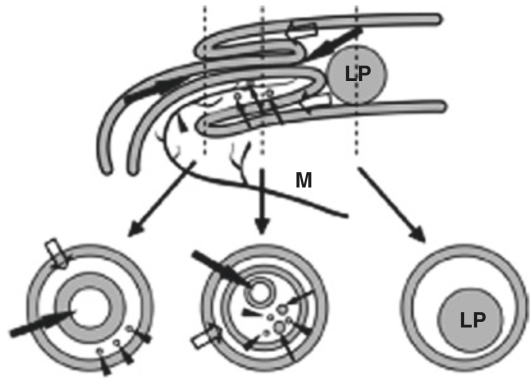

Fig. 7.5 Schematic drawings of intussusception. Longitudinal and serial cross-sectional diagrams of intussusception show invagination of one segment of the gastrointestinal tract (intussusceptum) (*thick solid arrows*) into the adjacent segment (intussuscipiens) (*open arrows*). Proximal cross-sectional diagram of intussusception (*bottom right*) shows two layers, although the classic appearance of three layers (*middle bottom*) is shown in midportion of intussusception. Note invagination of the mesentery, mesenteric vessels (*arrowheads*), and hyperplasic mesenteric lymph nodes (*thin solid arrows*). *LP* lead point, *M* mesentery. Reproduced with permission from [64]

appears as a complex soft tissue mass consisting of the outer intussuscipiens and the central intussusceptum (Fig. 7.5). Any tumor acting as the lead point of an intussusception may be outlined distal to the tapered lumen of the intussusceptum. The cause of intussusceptions in adults varies by location. Large bowel lead points are more frequently malignant than small bowel lead points.

7.2.4.1 Pregnancy Per Se

Currently, it is not known how does pregnancy contribute to the development of intussusception or is it just a coincidence. Most patients without the lead point are in the second or third trimester [17, 65–68]. The long-standing obstipation, common in pregnancy, as well as the direct pressure exerted by the gravid uterus upon the rectum in the direction of the sacrum, tends to produce this entity without the leading point.

7.2.4.2 Leading Point

Various pathologic conditions, as leading points, can be present and found as early as the eighth week of pregnancy [57]. These include hamartomatous polyp [59], lipoma [57], benign neurilemmoma [69], and primary non-Hodg-

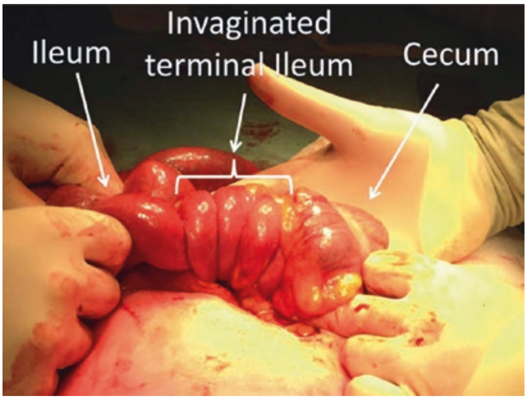

Fig. 7.6 The ileocecal intussusception in 8 weeks pregnancy. The terminal ileum was "telescoped" into the lumen of the cecum and the ascending colon. Reproduced with permission from [57]

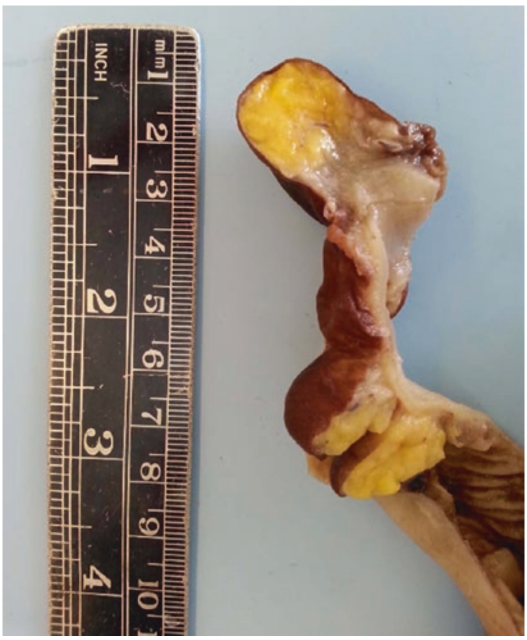

Fig. 7.7 Macroscopic cross sections showed several lipomatous tumors in the terminal ileum, located under the mucosa. Reproduced with permission from [57]

kin's lymphoma [70, 71]. Meckel's diverticulum is the most common [72]. Even the heterotopic pancreas was found as a cause of intussusception during pregnancy [13]. It is postulated that there is a relationship of the enlargement of a heterotopic pancreas with the hormonal changes in gestation [73]. In pregnancy, the most common is ileocecal intussusception (Figs. 7.6 and 7.7). When the colon has the leading point in pregnancy, it has a higher incidence of malignancy [74].

7.2.4.3 Bariatric Surgery

Retrograde (antiperistaltic) intussusception is rare but is the most common after gastric bypass in general population. The incidence is 0.07–0.15% after both laparoscopic and open RYGB [75, 76]. The mechanism of retrograde intussusception remains unclear. Although retrograde peristalsis occurs naturally in the intestinal system, retrograde intussusception does not occur. Variations in the configuration of jejunojejunostomy, i.e., antiperistaltic versus isoperistaltic, have also been suggested as a possible cause. The entry point is just below the jejunojejunostomy, and there is a characteristic absence of any identifiable leading point. The first retrograde jejunojejunal intussusception in pregnancy was described by Wax et al. in 2007 [77]. Retrograde jejunojejunal intussusception after LRYGB during pregnancy (Fig. 7.8) could have a higher incidence in comparison to general population. The period between prepregnancy LRYGB and intussusception is wide, 1–9 years [77, 78].

7.2.5 Clinical Presentation

The clinical presentation of adult intussusception varies considerably. Presentation depends on the:

- Location of intussusception
- Rapidity of obstruction
- Duration of intussusception
- Underlying cause

The most common symptoms of intussusception are abdominal pain, nausea, and vomiting; less frequent symptoms are melena, weight loss, and fever, which could be of long duration (several weeks to several months) if the intussusception is intermittent or partial, although the patient may occasionally present with complete mechanical obstruction with bowel gangrene [50]. Common physical findings include abdominal distention, decreased or absent bowel sounds, and abdominal mass [49, 58]. Making a

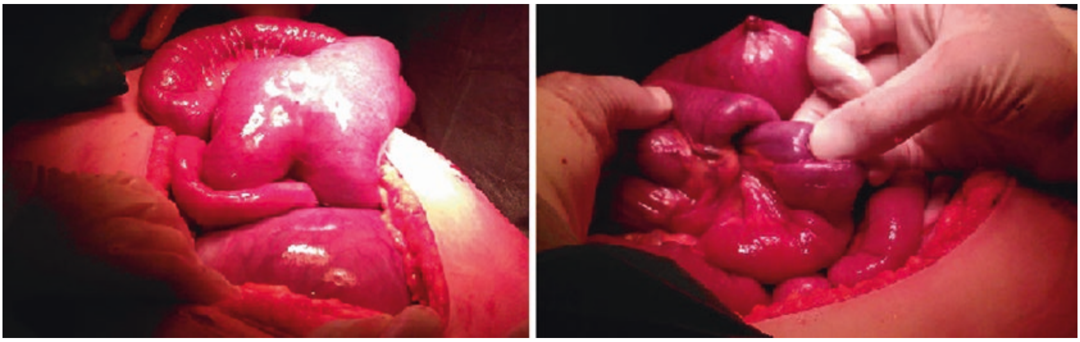

Fig. 7.8 Dilation of the small bowel, including the anastomosis. Gravid uterus is seen in the lower part of the laparotomy exposure (*left*); manual reposition of jejunojejunal intussusception (*right*). Reproduced with permission from [78]

diagnosis of intussusception in adults is equally tasking because the classical pediatric triad of intussusception (acute abdominal pain, palpable "sausage-shaped" mass, and "red currant jelly" stools) is seldom observed. In a pregnant woman, especially at the advanced stage of gestation, it may not be possible to palpate a mass [17]. Palpable mass can be found up to 22 weeks gestation [14, 58]. A malignant cause of intussusception is more likely to present with a shorter duration of symptoms. Sometimes the symptoms can resolve but can recur during the same pregnancy if partial or intermittent intussusception is present [17]. Symptoms of the rectoanal intussusception (internal rectal prolapse) are the sensation of incomplete evacuation; pressure toward the sacrum, which may increase with straining; very frequent stools, small, slimy and more or less mixed with blood and uncontrolled by internal medication; tenesmus; and absence of fever.

The implication of these is that there is often a delay in making a diagnosis. The additional diagnostic problem is when obstructive symptoms present in the puerperium. Symptomatology is the same as in general or pregnant population after normal vaginal delivery [62] or CS [63]. Suspicion should be raised if abdominal pain or distention occurs after a period of normal post-CS course or normal vaginal delivery. Difficulties after CS are encountered because: (1) symptoms are attributed to incisional pain and (2) ileus is attributed to early postoperative ileus or acute pseudo-obstruction [79]. Idiopathic postoperative intussusception is more common after abdominal operations and usually occurs within 2 weeks following surgery.

7.2.6 Differential Diagnosis

In addition to the standard differential diagnosis of intestinal obstruction, an associated medical complication such as acute pancreatitis, seen with afferent biliopancreatic limb obstruction after RYGB, may draw attention away from the inciting obstruction. The nonspecific nature of abdominal complaints early in the course of RYGB-associated obstruction may incorrectly be attributed to common obstetrical complaints such as morning sickness, hyperemesis, reflux, and uterine contractions.

7.2.7 Diagnosis

With the increasing use of ultrasound, CT, and improved methods for examining the small bowel, intussusception is currently diagnosed more frequently preoperatively. In the 11 reported cases of intussusception in pregnancy in the past 25 years, 55% were diagnosed preoperatively. Three cases were diagnosed by abdominal ultrasound, one by plain abdominal X-ray post-delivery, and one by abdominal MRI [56, 59, 65, 80]. In the puerperium, all diagnostic imaging modalities could be safely used [62, 63, 79].

7.2.7.1 Plain Abdominal X-Ray

Plain abdominal radiographs depend on the degree of intestinal obstruction. In complete obstruction, classic air–liquid level is seen as in any other cause of intestinal obstruction. Findings are typically and potentially misleadingly normal in retrograde intussusception after RYGB [77], despite some cases diagnosed with this modality.

7.2.7.2 Transabdominal Ultrasound

Abdominal sonography can make the diagnosis of an intussusception in an adult when the characteristic sign of a "target-like" lesion or "bull's-eye" lesion is shown, similar to the CT findings, and is sometimes enough for the definitive diagnosis without the necessity to do plain abdominal X-rays [80]. The classic features of intussusception include "target," "doughnut," or "crescent-in-doughnut" signs on a transverse view and the "pseudokidney" sign in the longitudinal view (Fig. 7.9) or multiple concentric rings of intussusceptum (Fig. 7.10) or multiple concentric vascular signals in thickened intussuscipiens (Fig. 7.11) [14, 59, 62]. The central echogenic area is produced by the mucosa of the intussusception, which is surrounded by a hypoechoic ring representing the walls of both the intussusceptum and the intussuscipiens [79]. This variability in appearance is largely due to the scanning level, the amount of intussuscepted mesentery, the degree of bowel wall edema, and the

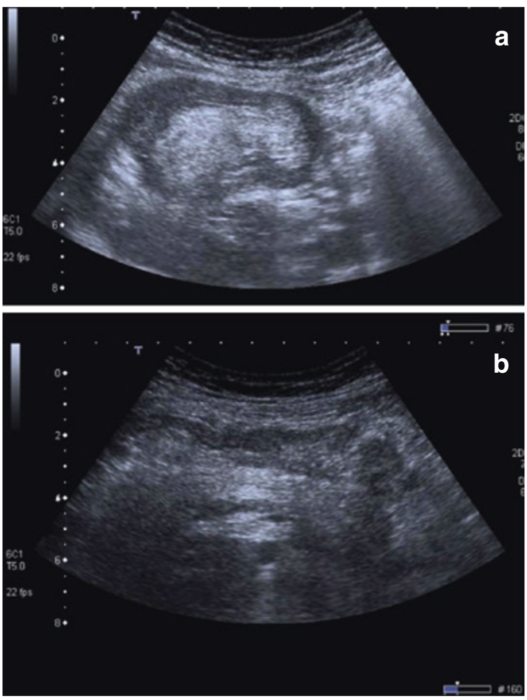

Fig. 7.9 (**a**) Transverse abdominal sonography: a "bull's-eye" or "doughnut" image with an echogenic center and a translucent rim is visible. (**b**) Longitudinal ultrasound scan showing the "pseudokidney" sign, representing the appearance of the intussusceptum and intussuscipiens. Reproduced with permission from [57]

Fig. 7.10 Jejunojejunal intussusception during late pregnancy. Transverse gray-scale sonogram showing multiple concentric rings (*arrows*) representing multiple layers of the innermost intussusceptum, intervening mesenteric fat, and vessels and outer intussuscipiens at the left of the fetal abdomen (*arrowheads*). Reproduced with permission from [59]

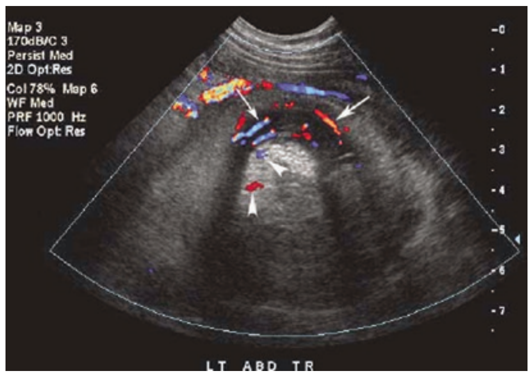

Fig. 7.11 Jejunojejunal intussusception during late pregnancy in a 33-year-old woman. Transverse color Doppler sonogram showing multiple concentric vascular signals in thickened intussuscipiens (*arrows*) and some vascular spots in the hypoechoic intussusceptum (*arrowheads*) and echogenic mesentery. Reproduced with permission from [59]

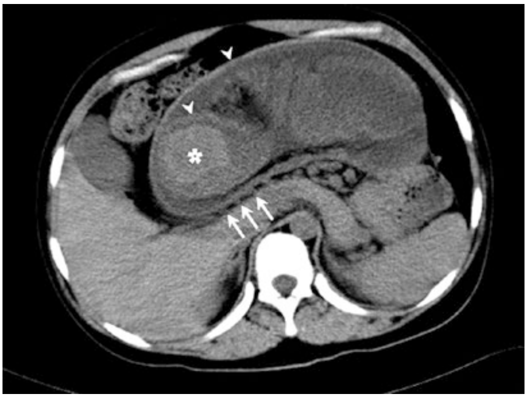

Fig. 7.12 Un-enhanced CT shows a "double-circle sign" of small intestine (*arrowheads*) with a neoplastic lead point (asterisk) and mesenteric vascular bands (*arrows*). Reproduced with permission from [81]

presence of a pathologic lead point and lymph nodes. Ultrasound is an operator-dependent whose utility may be limited by obesity and air in distended bowel loops.

7.2.7.3 Abdominal CT

Intussusception is well diagnosed on abdominal CT, which shows a pathognomonic bowel-within-bowel configuration (Fig. 7.12) with or without contained fat and mesenteric vessels [79]. Intussusception appears as a sausage-shaped mass when the CT beam is parallel to its longitudinal axis but as a target-like mass when the beam is perpendicular to the longitudinal axis [50].

In RYGB patients, abdominal CT is the investigation of choice. Plain abdominal films can be misleading and falsely reassuring due to the high level of obstruction. The great variability in the different gastric bypass techniques (antegastric or retrogastric Roux loop, in retrocolic or antecolic configuration) mandates the availability of the patients' operation notes to facilitate correct interpretation of the CT findings.

7.2.7.4 Abdominal MRI

Currently, instead of CT scan, MRI is used to eliminate ionizing radiation (Figs. 7.13 and 7.14). Barium reflux in the lumen of the space between the intussusceptum and intussuscipiens allows the coiled spring to be visualized. Abdominal MRI was first used to define intussusception during pregnancy in 1992 [56]. In 75% of patients, the leading point on abdominal MRI was not found [17, 19, 82].

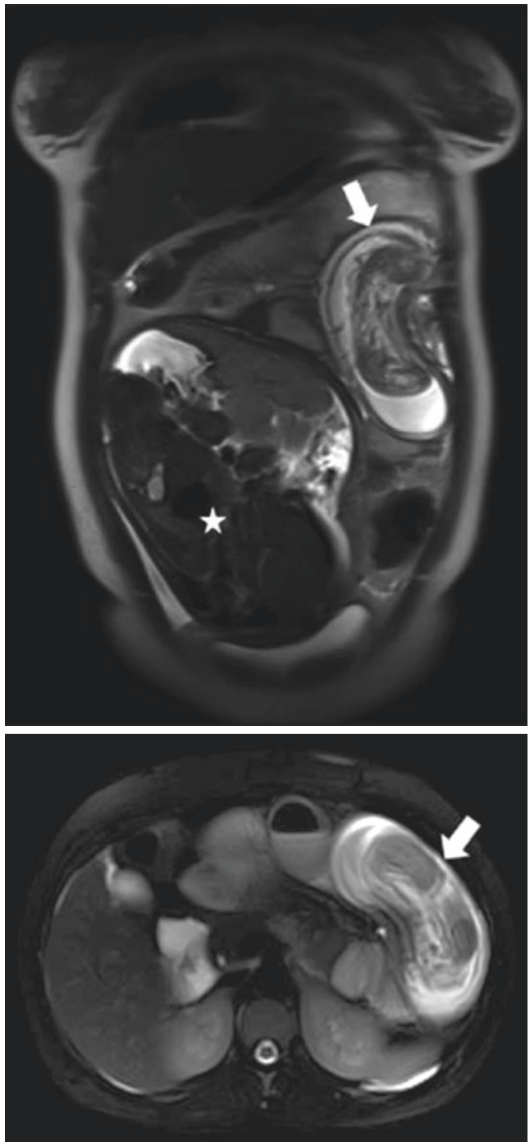

Fig. 7.13 A magnetic resonance imaging of intussusception. T2-weighted HASTE imaging, coronal section (**a**), shows a sausage-shaped intussusception (*arrow*) located superolateral to the gravid uterus (*star*). T2-weighted BLADE imaging, an axial section with fat saturation (**b**), shows the intussusception (*arrow*) located at the left side of the abdomen, anterolaterally to the left kidney. Also, note increased diameter of the affected intestinal segment with T2 hyperintense changes of the intestinal wall, indicative of edema. A lead point could not be identified. Reproduced with permission from [82]

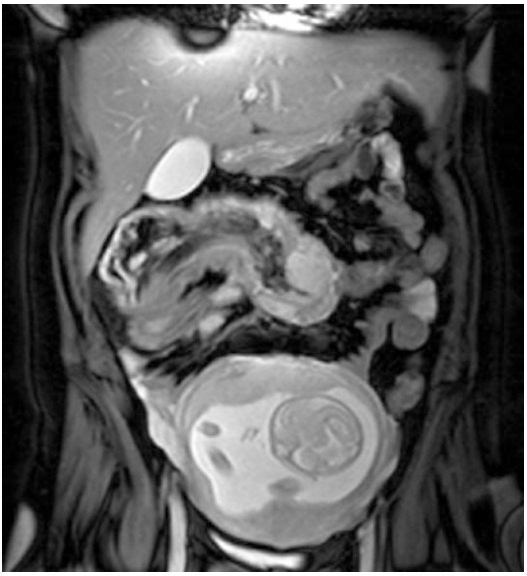

Fig. 7.14 MRI of intussusception in the epigastric region, with the gravid uterus inferior to and separate from the mass. Reproduced with permission from [65]

7.2.7.5 Additional Modalities

Rectoanal intussusception (internal rectal prolapse) is made primarily by defecography which is contraindicated in pregnancy. Anoscopy or rectoscopy easily reveals the intussuscepted fold and could differentiate it from incarcerated internal hemorrhoids. Dynamic pelvic MRI has the advantage of imaging all compartments of the pelvis and their interaction during defecation. Real-time dynamic transperineal ultrasound provides an additional means of evaluation of all compartments within the pelvis and their interaction at rest, as well as during straining and defecation.

7.2.8 Treatment

7.2.8.1 General Principles

Once the intussusception is suspected, emergency measures should be initiated. Immediate aggressive medical care within the first 24 h is necessary due to the high incidence of necrotic bowel in intussusception. There is an increased chance for death if this disorder is not treated within 48 h. Therapeutic principles for intussusception are the same as in nonpregnant population:

- Solve the intussusception itself
- Treat the cause of the intussusception if present

Conservative Treatment

The usual measures employed to deal with adhesive bowel obstruction such as blind nasogastric tube insertion have no place in RYGB patients as they can lead to bowel perforation at the gastrojejunostomy and false sense of decompression, while the biliopancreatic limb can still remain obstructed.

In colonic intussusception, malignancy and resection are more likely. Therapeutic barium enema can be tried in a few selected cases where the underlying pathology is known or not present [79]. Rectal intussusception treatment from 1879 (see Sect. 7.2.5) consisted of copious injections of cold water made with considerable force. These unfolded the invagination and produced natural dejections. In some patients, small bowel intussusception may be an incidental finding. Careful observation may be indicated if imaging does not reveal an identifiable lead point, vascular compromise, or bowel obstruction [79].

Surgical Treatment

Almost all patients are explored by laparotomy, but recently laparoscopy is more frequently used to minimize abdominal wall trauma and shorten postoperative hospital stay [63, 79]. This is important to facilitate earlier return to normal life and maternal care about the newborn baby.

After exploration further procedure depends on the viability of the intestine and the presence of the lead point. The manual reduction can be attempted in small bowel intussusception if the segment involved is viable and if malignancy is not suspected, palpated, or checked with intraoperative enteroscopy [63]. The manual reduction should be performed in a form of pushing the intussuscipiens rather than pulling the bowel due to lower risk of bowel wall tearing. Resection of the bowel segment is indicated when [62]:

Fig. 7.15 Jejunojejunal intussusception during late pregnancy. Jejunojejunal intussusception of about 80 cm in length shown as a sausage-shaped mass comprising the swollen intussuscipiens with an invaginating intussusceptum of more proximal loops. Pedunculated polypoid mass was hamartomatous polyp. Reproduced with permission from [59]

- Gangrenous bowel
- Recurrent intussusceptions
- Leading point present

When the leading point is present and resected, further therapy depends on the pathohistological diagnosis (Fig. 7.15).

7.2.8.2 Bariatric Surgery

Blind nasogastric tube insertion is contraindicated in RYGB patients (see Sect. 7.2.7.1) as it can lead to bowel perforation at the gastrojejunostomy and false sense of decompression, while the biliopancreatic limb can still remain obstructed.

Surgical treatment involves resection of jejunojejunostomy and reconstruction of a new jejunojejunostomy distally. Despite this, recurrences can occur. Simple reduction and reduction with plication of the bowel lead to higher recurrence rate. To prevent the occurrence of jejunal intussusceptions after RYGB, sleeve gastrectomy could be a better option for pregnant patients or those who would like to become pregnant [83].

7.2.9 Prognosis

As early as 1937, it was stated that the mortality was higher in all stages of pregnancy [60]. Prognosis depends on the state of the bowel. Maternal prognosis, with the indication for resection due to ischemic bowel and when no resection (viable bowel without the lead point) is necessary, is excellent [57, 62, 63, 79, 82]. Higher rates of spontaneous abortion and preterm labor are present [57], especially if perforation with peritonitis occurs. If intussusception presents during puerperium, it is easier to indicate diagnostic imaging modalities with radiation; therefore, the diagnosis could be made earlier. The problem is that intussusception is sometimes mistaken for post-delivery ileus delaying the diagnostic workup.

7.3 Transvaginal Instrumental Uterine Perforation

7.3.1 Introduction

Let alone the fact that abortion is an extremely sensitive topic everywhere, it is perhaps unreasonable to expect reliable data about abortion practices in a country such as India where even vital registration—the recording of births, deaths, and marriages—is far from complete and accurate [84]. Most illegal abortions are conducted in the rural areas of developing nations without adequate facilities and by persons with no knowledge of anatomy who operate with non-sterile instruments with increased percentage of mortality and morbidity [84]. One important, although rare, complication is small bowel obstruction through uterine wall perforation. Obstructions of the large intestine are rare due to its fixed position; therefore, complications with large bowel mostly include instrumental perforations. One of the first published cases of small bowel obstruction in the form of evisceration through vaginal introitus is from 1907 by Werelius [85]. The data in this section are from the review by Augustin et al. published in 2013 with cases from 1907 to 2012 [86]. Several other cases were published afterward [87].

7.3.2 Incidence

First-trimester surgical abortion (as opposed to prostaglandin medical abortion) is one of the most frequently performed procedures in the United

States: 853,485 procedures were performed in 2001 [88]. Minor complications (0.846%) secondary to first-trimester surgical abortion are managed as outpatient procedures including mild infection, resuctioning on the day of the procedure or subsequent resuction, cervical stenosis, cervical tear, underestimation of gestational age, and convulsive seizure after local anesthesia [89]. Major complications (0.071%) require hospitalization after the first-trimester surgical abortion including incomplete abortion, sepsis, uterine perforation, vaginal bleeding, inability to complete abortion, and combined (heterotopic) pregnancy [89]. Uterine perforation during an abortion is rare, with a reported rate of 0.05–1.9% [90–93].

There are, fortunately, around 30 case reports of small bowel obstruction through uterine perforation after vacuum abortion, surgical abortion, or unsafe abortion published. Almost all cases were during the first trimester [94]. The distribution through the trimesters is contrary to the fact that second-trimester abortion has a higher rate of complications than abortions performed in the first trimester [91, 93, 95]. The extremely rare incidence of small bowel obstruction after uterine perforation due to surgical abortion is due to:

- The rare occurrence of instrumental uterine perforation
- Spontaneous healing of most (recognized and unrecognized) uterine perforations without further complications [96]
- Immediate laparotomy/laparoscopy in 47–84% of cases with recognized complicated uterine perforation [92]
- An unknown number of cases not published in the medical literature
- Prehospital mortality, especially in undeveloped countries [97]

7.3.3 Risk Factors

In an attempt to identify factors potentially leading to uterine perforation, several authors determined that the level of training was the strongest statistically significant risk factor for perforation [98, 99]. Other factors were advanced maternal age, greater parity, retroverted uterus, history of prior abortion or CS, history of previous cone biopsy, failure to use ultrasound, and underestimation of the duration of pregnancy [90, 91, 93, 100, 101]. Uterine perforations are mostly located at the uterine fundus, presumably caused by the introduction of cervical dilators [102]. Hence, difficulty during cervical dilatation also has been associated with a higher perforation rate, and some authors recommend prostaglandin use to aid in dilatation of the cervix [91, 93]. Additionally, prostaglandins have the benefit of contracting the uterus, which may help decrease the perforation rate [92].

Currently, there are no known risk factors for small bowel obstruction after uterine perforation. Unfortunately, there are insufficient data for the conclusions, but four factors could increase the incidence rate [86, 100, 103, 104]:

- Failed medical abortion
- Curettage for retained parts of the placenta after a previous pregnancy
- The diameter of uterine perforation
- Multiple pregnancies

7.3.4 Mechanisms of Small Bowel Obstruction

There are four mechanisms of small bowel obstruction after uterine perforation.

Most common is due to small bowel prolapse (Fig. 7.16) through uterine perforation by three

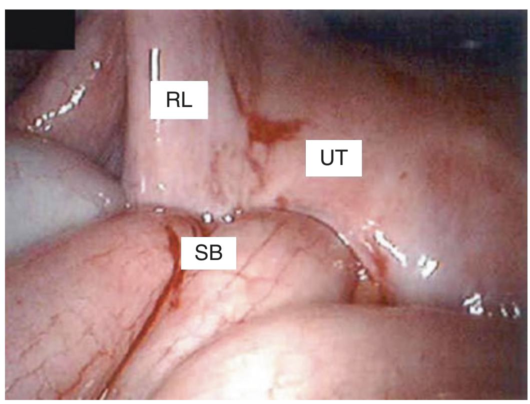

Fig. 7.16 A defect in the anterior myometrium of the uterus (*UT*) at the level of the left round ligament (*RL*), through which the small bowel (*SB*) has become incarcerated. Reproduced with permission from [105]

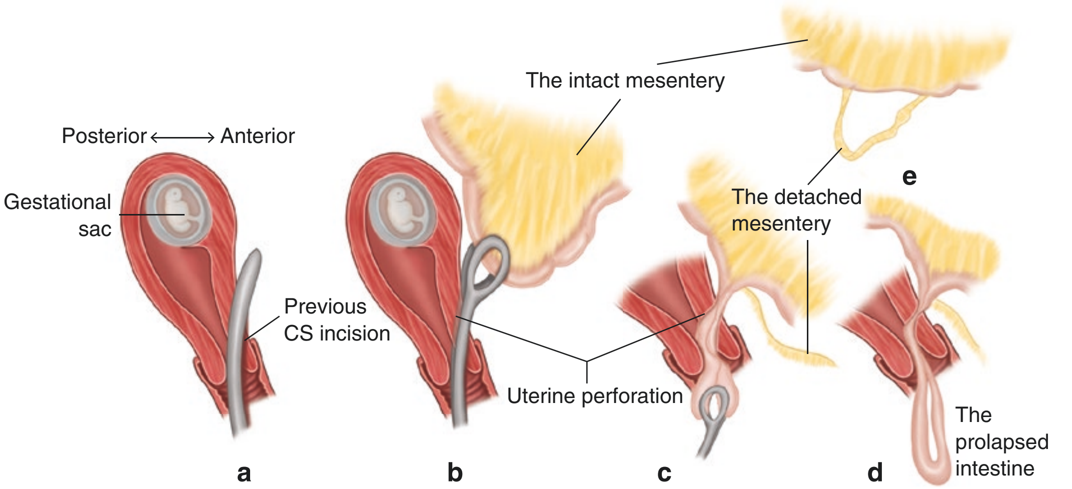

Fig. 7.17 Schematic of the event. (**a**) The anterior uterine body wall was perforated with the Hegar dilator. The previous Cesarean section incision was normal. (**b**) The forceps were extracted from the uterus through the perforation, grasping the ileum. (**c**) The ileum was pulled through the perforation site. The mesentery was detached when the ileum was pulled through the narrow perforation site. (**d**) The ileum prolapsed into the vagina. The ileum was strangulated at the perforation site. (**e**) The mesentery was completely separated from the bowel, resulting in ileal necrosis. Strangulation at the site of narrow perforation hole (**d**) may also have caused ileal necrosis. Reproduced from [87] under the CC Attribution License

mechanisms: (1) spontaneously through larger uterine perforation, during episodes of increased intra-abdominal pressure, (2) due to inadvertent aspiration [94, 105–109], and (3) the most extensive type when the small bowel loops are pulled out of vaginal introitus (Fig. 7.17) [97, 98, 104, 110]. Two explanations for these vigorous manipulations follow. First, in attempts to evacuate the parts of the fetus, the physician pulls the part of the bowel instead. In the other similar circumstances, the small bowel is mistaken for the umbilical cord and freely pulled out.

The second mechanism is where uterine perforation contains incarcerated herniated omentum and a band attached to the omentum strangulates a segment of the extrauterine small bowel, producing obstruction (Fig. 7.18) [90] or even can produce small bowel volvulus around the fibrotic band or omental band.

The third mechanism is when the small bowel is entrapped in adhesions at the site of uterine perforation [112]. The fourth mechanism is Richter hernia-type obstruction when the antimesenteric wall of the intestine

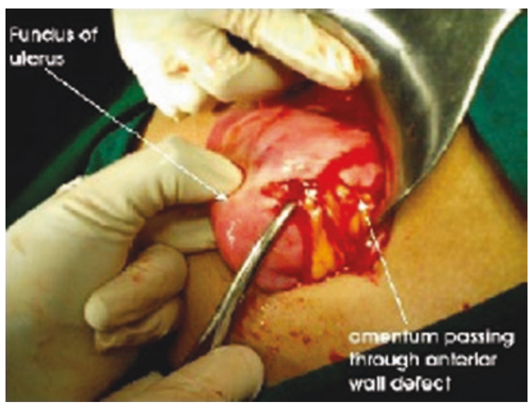

Fig. 7.18 Greater omentum incarcerated through the anterior wall defect of the uterus. Reproduced with permission from [111]

protrudes through a defect in the uterine wall [108]. The explanation for symptomless Richter type of small bowel obstruction follows. During the first pregnancy (2 years previously), a dilatation and curettage had been performed 4 weeks after delivery to remove the retained placenta. During instrumentation, the uterine wall perforation occurred with the formation of

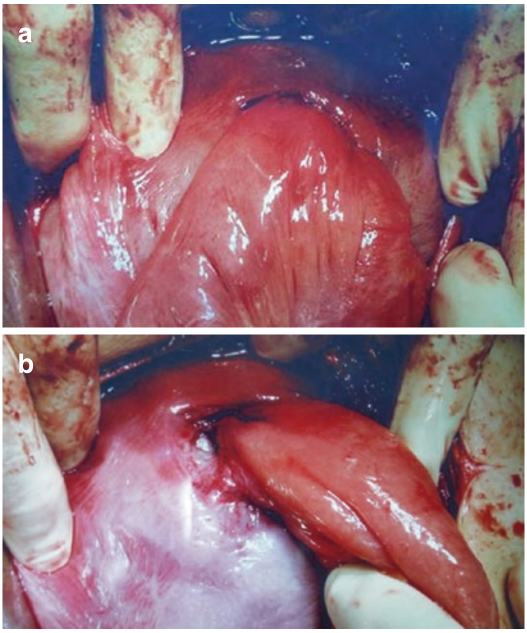

Fig. 7.19 (**a**) Richter type of a hernia when the antimesenteric wall of the intestine protrudes through a defect in the uterine wall causing a partial obstruction which evolves to complete obstruction during a subsequent pregnancy. (**b**) The dilated afferent loop is pulled aside to reveal the depth of the uterine perforation. Reproduced with permission from [103]

Richter type of a hernia but without ischemia of the small bowel wall. In this second pregnancy at an advanced stage, the growing uterus that made compression and occlusion of the small bowel was fixed to the uterus previously as Richter type of a hernia (Fig. 7.19). It is important to note that most (83%) large bowel injuries were associated with posterior uterine wall perforation, whereas 60% of the small bowel injuries were associated with anterior wall or uterine fundus perforation [84].

7.3.5 Clinical Presentation

The uterine perforations are usually recognized during the procedure (dilatation and curettage). If the patient signals significant lower abdominal pain, associated injuries should be sought [109]. If unrecognized, the majority of patients have an uncomplicated course with the spontaneous healing of uterine perforations (see Sect. 7.3.2). The type and time of presentation depend on two pathophysiologic processes that could coexist (iatrogenic bowel perforation is excluded):

1. Mechanism of small bowel obstruction
2. Associated bleeding:
   (a) From the uterine wall around perforation
   (b) From the mesentery detached from its bowel [113]

1. The mechanism of small bowel obstruction dictates the severity, intensity, and time of presentation of obstruction. Duration of symptoms due to adhesions is variable, from 4 days to 4 months [86]. These symptoms cause the delay in diagnosis because the patients with partial obstruction are commonly managed conservatively [109]. Adhesions can cause partial or progressive small bowel obstruction from nonspecific symptoms including abdominal pain with/without distention to vomiting, (paradoxical) diarrhea, or absence of flatus and/or stool in later stages. Fever and chills are present in the advanced stage when small bowel gangrene ensues. A serious consideration of this possibility is necessary, as the intrauterine or intravaginal location of strangulated/detached bowel may mask the characteristic peritoneal signs [90]. Presentation after 2 years was due to Richter type of a hernia that is unpredictable. It can incarcerate initially with early presentation, or another pathophysiologic event should be present for initiation of obstruction. Probably it depends partly on the size of uterine perforation [103]. Richter type of incarceration can produce enterouterine fistula (see Sect. 11.8).

   Ischemic bowel perforation is pathophysiologically different from the direct bowel injury during instrumental uterine perforation. Such injuries develop clinical picture mostly within few hours after the procedure [114]. If the incarceration of the bowel through the uterine wall is present and not recognized during an abortion and if complete obstruction due to bowel prolapse through the uterine wall

Fig. 7.20 Evisceration with resultant congested and edematous loops of the small bowel through vaginal introitus 2 h following evacuation of the uterus done for an incomplete abortion. Reproduced with permission from [110]

is the cause, then all patients presented 1–48 h after uterine instrumentation [86]. If the small bowel is prolapsed in a form of vaginal evisceration, the diagnosis is evident clinically due to the transvaginal small bowel prolapse (Fig. 7.20).

2. Any mechanism of small bowel obstruction could be accompanied by hemorrhage from either uterine wall perforation or detached mesentery from the bowel. Clinically, hemorrhage from uterine wall perforation is evident due to transvaginal bleeding, but mesenteric bleeding can present either with transvaginal or intra-abdominal bleeding or both. An intra-abdominal bleeding presents as abdominal pain and should be always looked for because the pain can be attributed to abdominal pain caused by coexisting small bowel obstruction with abdominal distention. It is difficult to conclude the hemorrhage or small bowel obstruction dominant in these patients because variations in severity of developing obstruction and variations in severity of bleeding could be present. In the study by Augustin et al., 39% of patients were hypotensive [86].

7.3.6 Diagnosis

7.3.6.1 Laboratory Findings

Significant bleeding can be confirmed or excluded with complete blood count. Blood urea nitrogen and creatinine define the volemic state of the patient. All laboratory findings are needed for the correction of the metabolic derangements and do not delay the emergent operation if indicated, such as when vaginal evisceration is present.

7.3.6.2 Plain Abdominal X-Ray

If evisceration is not clinically evident, the diagnosis should be suspected when air–liquid levels of small bowel are evident on plain abdominal X-ray in a patient after transvaginal intrauterine instrumentation.

7.3.6.3 Abdominal Ultrasound

Knowledge of the typical appearance of the uterus after a first-trimester surgical abortion is helpful in recognizing an abnormal pelvic ultrasound. In the emergent presentation, ultrasound is the preferred diagnostic modality, but the normal appearance of the uterus after a first-trimester surgical abortion can be quite variable. A small number of imaging studies have documented the appearance of the uterus after a first-trimester surgical abortion [115–117]. Follow-up with ultrasound after a first-trimester surgical abortion showed that near 59% of patients had a varying amount of intrauterine material, initially appearing hyperechoic and then later iso- or hypoechoic [117]. No material seen resembled retained fetal parts or placental material. The time for the return of the endometrial stripe to baseline appearance was variable, ranging 1–14 days. Similarly, within 1 week of the procedure, only 23% of patients demonstrated reversion to a thin endometrial stripe, 50% displayed a thick endometrial stripe (7–19 mm), and 27% an endometrial stripe >20 mm or with very irregular echogenicity >14 mm [116]. These investigators also described a trend toward hyperechoic endometrial contents earlier in the week versus hypoechoic contents later in the week, presumably due to liquefying endometrial contents. The appearance of endometrium after the first menstrual period reverted to

normal in all patients. Patient demographics such as gravidity or date of first-trimester abortion did not correlate with the appearance of the uterus.

Ultrasound appearance of uterine perforation with suspected bowel entrapment was first reported in 1983 by Dunner et al. [107]. A defect in the uterine wall could be detected with the transabdominal ultrasound. The tubular-shaped irregular tissue could be seen within the endometrial cavity, with a small echoic focus suggesting the presence of air (Fig. 7.21). An abnormally increased amount of echogenic free fluid could be seen in the cul-de-sac [105]. Transvaginal sonography is a convenient tool in aiding in the diagnosis. Findings of free fluid in the pelvis, loops of bowel within the myometrial wall, extra-uterine fetal parts, or intraoperative presence of the curette within the myometrium have all been used to confirm uterine perforation [118]. Ultrasound of the pelvis could delineate bright, serpiginous, fluid-filled tubular structures within the endometrial cavity (Fig. 7.22). The adjacent material of increased echogenicity could be suggestive of fat. Color Doppler would not show blood flow in these structures, and no peristalsis would be seen in the intrauterine contents [105].

Except for defining a uterine perforation, an abdominal ultrasound should confirm or exclude retained intrauterine fetal parts or parts of other intra-abdominal organs [119].

7.3.6.4 Abdominal CT

The first reported CT diagnosis of incarcerated bowel in a uterine perforation was in 2008 by both Dignac et al. (incarcerated appendix) and Chang et al. [100, 101]. Abdominal CT has an important diagnostic role when ultrasound is ambiguous or if non-gynecologic pathology is suspected. Although the uterine wall can hinder visualization of intrauterine bowel loops, the bowel's mesentery can be well visualized on CT due to its fatty nature and should be a red flag for intrauterine bowel [101]. CT scan can delineate bowel loops within the uterus (Fig. 7.23).

7.3.6.5 Abdominal MRI

Recently, abdominal MRI has been utilized to assess the endometrial cavity after the first-trimester surgical abortion [115], but this is not routinely performed on an emergent basis. There is only one case showing incarceration of the

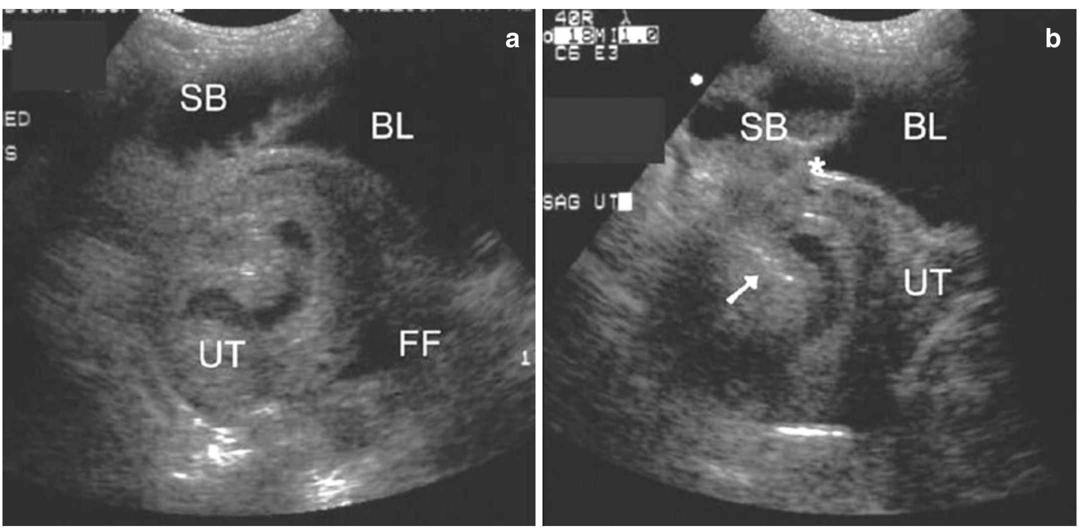

Fig. 7.21 (**a**, **b**) Transabdominal pelvic ultrasound images demonstrate a retroverted uterus (*UT*) adjacent to the urinary bladder (*BL*) with adjacent fluid-filled small bowel (*SB*) closely apposed to an interrupted uterine wall (*asterisk*). A tubular structure is seen within the uterus. A small amount of anechoic free fluid (*FF*) is seen in the cul-de-sac. Linear echogenicity (*arrow*), consistent with the appearance of gas, is adjacent to the abnormal intra-uterine tubular structure. Reproduced with permission from [105]

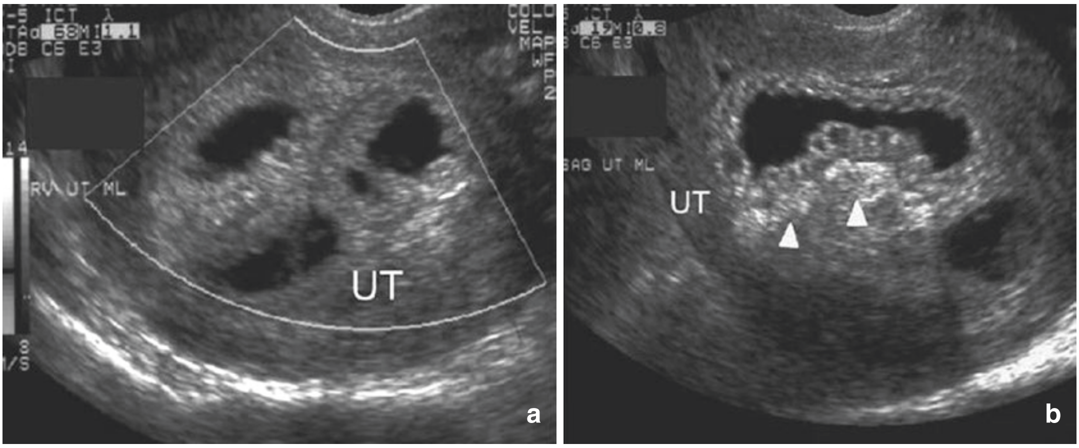

Fig. 7.22 (**a**) Transvaginal pelvic ultrasound transversely demonstrates multiple tubular structures containing anechoic fluid within the uterine cavity (*UT*); (**b**) sagittally, echogenic material (*arrowheads*), suggesting the presence of fat, is adjacent to the intrauterine tubular structure. Reproduced with permission from [105]

Fig. 7.23 Pelvic CT scan taken after the failure of conservative treatment. Intrauterine mass is an incarcerated small bowel. Reproduced from [100] under the CC Attribution License

greater omentum in the uterine perforation without bowel obstruction [120].

7.3.7 Treatment

7.3.7.1 Conservative Treatment

Uterine perforations are divided into uncomplicated and complicated. Most uterine perforations recognized during abortion without complications could be managed conservatively [92, 93], with a significant number of these perforations detected during combined laparoscopy [96]. This implies that the true perforation rate may be underreported and underrecognized without severe consequences to patients, suggesting that conservative management of uncomplicated uterine perforations with close observation is adequate [92, 101, 108].

7.3.7.2 Surgical Treatment

The diagnosis or even suspicion of intrauterine bowel/bowel injury (complicated uterine perforation), however, mandates emergent exploration. Emergent exploration prevents progression of bowel distention with the development of ischemic necrosis and/or subsequent bowel perforation. Intravenous fluids and antibiotics (ceftriaxone 2 g and metronidazole 500 mg as starting doses) should be immediately administered.

During exploration, the bowel should be reduced into the peritoneal cavity and evaluated for vitality. The involved herniated bowel may be strangulated, have direct bowel wall trauma, or may be devascularized by coexistent injury or incarceration of the mesentery [109]. In all cases of vaginal evisceration, resection was necessary. In 14/18 patients, the length of resected small bowel was measured. In only one patient, the resected length was 30 cm, and in all others, the minimal resected length was 100 cm. In 56% of patients, more than 200 cm was resected. In the subgroup of patients with ileal adhesion (three patients), the resection of ischemic bowel was necessary for two patients (67%). The question is whether the bowel could be saved with earlier diagnosis and operation earlier in the course of the

disease, but the answer cannot be made because of the lack of all necessary data. Diversion in the form of a stoma was made in only one patient with complete small bowel resection. It should be performed in patients with hemorrhagic shock or in sepsis due to late presentation with gross purulent and/or fecal contamination of the peritoneal cavity. If isolated small bowel obstruction is present, resection with anastomosis is preferred treatment in patients without peritonitis [86].

When the vaginal wall is the cause of small bowel evisceration, the vital bowel can be manually reduced intraperitoneally. Such cases are not possible with uterine perforation because the uterine defect is difficult to close transvaginally. In addition, one must be sure that except for defining a uterine perforation, an abdominal ultrasound should confirm or exclude retained intrauterine fetal parts or parts of other intra-abdominal organs [119] that preclude transvaginal route for definitive operation.

7.3.7.3 Gynecologic/Obstetric Procedures

Uterine perforation/laceration should be repaired after treatment of small bowel injury. Sometimes uterine perforation should be enlarged for easier pulling of the bowel into peritoneal cavity minimizing the possibility of further bowel and mesenteric damage (two patients) [106, 113]. Rarely, a hysterectomy is required if the uterus is necrotic or irreparable [114, 118]. Hysterectomy was performed in 4/7 patients from the first half of the century and none after 1966.

> The uterine debridement with suture repair of the uterine defect is the procedure of choice [86].

There is a description of one patient without repair of uterine perforation where perforation size was 1 cm [90].

Preoperative consultation with the patient for permanent sterilization should be done because during operation, short additional procedure could prevent repeating of complications of further abortions. During surgical exploration, a search for mutilated fetus should be done [121] with definitive curettage if necessary. Perioperative antibiotics should be administered as in bowel obstruction in general. During follow-up, ultrasonogram of the uterus and βHCG measurement should be performed to eliminate the possibility of retained products of conception [121].

7.3.8 Prognosis

Worldwide, there are 30–50 million induced abortions that result in the death of 80,000–110,000 women of which an estimated 34,000 are in sub-Saharan Africa [99]. Appropriately timed surgical intervention in complicated uterine perforation is crucial to decrease morbidity and mortality rates. Available data show the survival rate of 93% (two deaths) during the whole century (1907–2012). One patient died due to massive small bowel necrosis where resection with high jejunostomy was made. The girl left the hospital against medical advice for social and family reasons and died [84]. The assumption is that high jejunal stoma with high output caused dehydration and electrolyte imbalance, finally causing death. The second patient had additional sigmoid colon laceration treated during initial operation with resection and anastomosis. The patient became febrile and deteriorated on the fourth postoperative day. The assumption is that dehiscence of colorectal anastomosis with diffuse stercoral peritonitis and subsequent septic shock with multi-organ failure developed [104]. The results of this study show that excellent prognosis is present throughout the whole century due to several reasons:

1. The population of these patients is young, mostly without comorbidities, and can compensate significant pathophysiologic stress such as small bowel obstruction and/or perforation sometimes accompanied by various degrees of hemorrhage. Such conditions could be deleterious for old people, especially with significant comorbidities.
2. Most patients present with evident small bowel obstruction either clinically as vaginal evisceration (60%) or during first 48 h with

small bowel in the uterine wall (23%) mostly diagnosed quickly and accurately with pelvic sonography. Small bowel obstruction in remaining patients was confirmed with plain abdominal X-ray before perforation ensued.
3. Complications of small bowel resection in young, healthy patients without advanced atherosclerosis are rare, and even long segmental resections have a good long-term prognosis.

7.4 Adhesions

7.4.1 Definition and Classification

Peritoneal adhesions are pathological bonds usually between the omentum, the loops of bowel, and the abdominal wall. These bonds may be a thin film of connective tissue, a thick fibrous bridge containing blood vessels and nerve tissue, or a direct contact between two organ surfaces [122]. According to their etiology, peritoneal adhesions may be classified as congenital or acquired, which can be postinflammatory or postoperative (the most frequent) [123]. Among postoperative adhesion formation, three processes may be distinguished: *adhesion formation* (adhesions formed at operative sites), *de novo adhesion formation* (adhesions formed at nonoperative sites), and *adhesion reformation* (adhesions formed after the lysis of previous adhesions) [124]. One classification distinguishes two main types of postoperative peritoneal adhesions. Type I or de novo adhesion formation concerns adhesions formed at sites that did not have previous adhesions, including type IA (no previous operative procedure at the site of adhesions) and type IB (previous operative procedures at the site of adhesions). Type II involves adhesion reformation, with two separate subtypes: type IIA (no operative procedure at the site of adhesions besides adhesiolysis) and type IIB (other operative procedures at the site of adhesions besides adhesiolysis) [125].

7.4.2 Incidence

Intra-abdominal adhesions are associated with 60–77% of intestinal obstruction in pregnancy [6, 8, 9] due to adhesions from previous abdominal surgery, pelvic surgery, or pelvic inflammatory conditions [6]. Around 50% had a previous appendectomy. Obstruction is mostly located on the small bowel, with isolated cases of adhesive large bowel obstruction in pregnancy [126]. Terminal ileum is the most common location of adhesive obstruction on small bowel [127–130]. The incidence of intestinal obstruction caused by adhesions during stages of pregnancy is [55]:

- First trimester: 6%
- Second trimester: 27%
- Third trimester: 44%
- Postpartum: 21%

7.4.3 Pathophysiology

7.4.3.1 Postoperative Adhesion Formation

Aside from the normal peritoneal regeneration, the process of postoperative peritoneal adhesion formation may be considered as the pathological part of healing following any peritoneal injury, particularly due to abdominal surgery [123]. The balance between fibrin deposition and degradation is crucial in determining normal peritoneal healing or adhesion formation (Fig. 7.24). When the fibrin is completely degraded, normal peritoneal healing may occur. In contrast, incompletely degraded fibrin may serve as a scaffold for fibroblasts and capillary in growth to form peritoneal adhesions.

Peritoneal healing differs from that of other epithelial tissues. In the healing process, the reepithelialization of peritoneal surfaces occurs simultaneously throughout the surgical site, because mesothelial cells migrate into the supportive matrix and initiate multiple sites of repair [131]. This is in contrast to epidermal repair, which gradually heals from wound borders. The mesothelial covering of defects occurs in approximately 3 days, and complete surface repair of the peritoneum is usually completed in 5–8 days. Adhesion formation is related to suture material, tissue devascularization, ischemia, infection, the amount of manipulation, and degree of aseptic

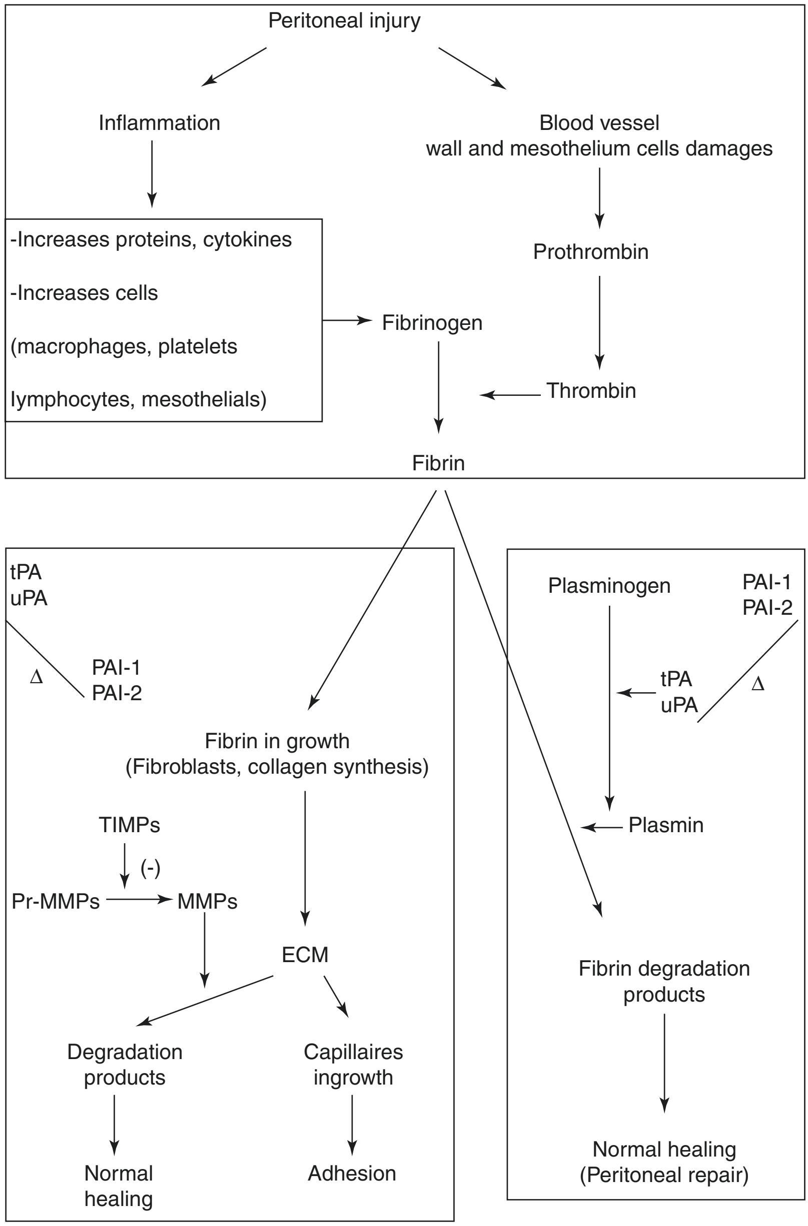

Fig. 7.24 Balance between plasminogen activators and plasminogen inhibitors. *TIMP* tissue inhibitors of metalloproteinases, *MMP* matrix metalloprotease, *ECM* extracellular matrix, *tPA* tissue-type plasminogen activator, *uPA* urokinase-type plasminogen, *PAI* plasminogen-activating inhibitor. Reproduced with permission from [135]

technique [132, 133]. The normal reparative process is profoundly influenced by ischemia. As so many factors are involved in this complex process, the contribution of peritoneal closure or non-closure to adhesion formation may be insignificant [134].

7.4.3.2 Uterine Enlargement During Pregnancy

As the uterine fundus arises out of the pelvis, intraperitoneal adhesions may produce initially a partial bowel obstruction, which may become complete as the uterine bulk increases [136].

7.4.3.3 Previous Appendectomy

Around 50% of patients with adhesive obstruction had the previous appendectomy. None of the case reports described neither the technique of appendectomy nor the stage of appendicular inflammation. Obstruction most commonly appears during the first pregnancy after surgery for acute appendicitis. In a significant number of cases, appendectomy was performed more than 9 years before the presentation of adhesive obstruction in pregnancy. Terminal ileum is the most common site of obstruction during pregnancy [129, 130] and puerperium [127]. The obstruction of the long loop of the sigmoid colon occurred 10 years after appendectomy [126]. A possible explanation is sudden changes in the position of bowel loops during uterine enlargement in pregnancy or after CS or vaginal delivery. These changes cause bowel rotation around the adhesive bend(s) or kinking of the bowel.

7.4.4 Prevention

These prevention strategies can be grouped into four categories: general principles, surgical techniques, mechanical barriers, and chemical agents [137].

7.4.4.1 Surgical Technique

Peritoneal damage should be avoided by careful tissue handling, meticulous hemostasis, continuous irrigation and avoiding unnecessary drying, ineffective use of foreign bodies, and suturing or clamping of tissue. The use of fine and biocompatible suture materials, atraumatic instruments, and starch-free gloves is recommended. The use of starch-powdered gloves is associated with an increased risk of extensive postoperative peritoneal adhesions. Foreign bodies most frequently found in postoperative adhesions are: surface powders from surgical gloves; lint from packs, drapes, or gowns; wood fibers from disposable paper items; and suture materials. However, in the absence of an additional peritoneal injury, foreign bodies are an infrequent cause of adhesion induction. Some intraoperative techniques, such as avoiding unnecessary peritoneal dissection or avoiding closure of the peritoneum, should be applied. Non-closure or closure of the peritoneum did not show the difference in peritoneal adhesion formation. However, grafting or suturing peritoneal defects may increase peritoneal ischemia, devascularization, and necrosis, predisposing the site to decreased fibrinolytic activity and increased adhesion formation. Furthermore, surgical trauma should be reduced as much as possible. The surgical approach (open vs. laparoscopic) could play an important role in the development of adhesions. The laparoscopic approach is associated with a significantly lower incidence of postoperative peritoneal adhesions or adhesion-related readmissions. Adhesion formation increases with the duration of CO_2 pneumoperitoneum and insufflation pressure. The benefits of heated humidified CO_2 insufflation (37 °C and 95% relative humidity, physiological conditions) have been reported to lessen adhesion formation. Furthermore, CO_2 pneumoperitoneum increases postoperative peritoneal adhesions in a time- and pressure-dependent relationship and that this increase is reduced by the addition of 2–4% oxygen, suggesting peritoneal hypoxia as the driving mechanism.

7.4.4.2 Mechanical Barriers

Liquid or solid mechanical barriers may prevent postoperative peritoneal adhesion formation by keeping peritoneal surfaces separate during the 5–7 days required for peritoneal reepithelialization. They prevent contact between the damaged serosal surfaces for the first few critical days. There are nonabsorbable and bio-absorbable films, gels, or solid membranes, but all these substances did not lessen postoperative adhesion formation significantly.

7.4.4.3 Chemical Agents

Chemical agents generally prevent the organization of the persisting fibrin, by fibroblastic proliferation inhibition. Many agents are used to inhibit this proliferation such as nonsteroidal

anti-inflammatory drugs, corticosteroids, calcium channel blockers, histamine antagonists, antibiotics, fibrinolytic agents, anticoagulants, antioxidants, hormones, vitamins, colchicines, and selective immunosuppressors. There was no difference and no clinical effectiveness of almost all these agents. In vitro studies have demonstrated that vitamin E has antioxidant, anti-inflammatory, anticoagulant, and antifibroblastic effects and decreases collagen production. It has been found to be effective for reducing adhesion formation. Vitamin E, administered intraperitoneally, is as effective as carboxymethylcellulose membrane in preventing postoperative adhesions.

7.4.5 Diagnosis

Diagnostic workup is the same as for every patient presenting with symptoms and signs of bowel obstruction no matter what the cause and is described previously (see Sect. 7.1). On plain abdominal X-rays adhesions are not visible. Sometimes thick adhesive bands can be visualized on abdominal CT (Fig. 7.25) and confirmed intraoperatively (Fig. 7.26).

7.4.6 Treatment

7.4.6.1 Conservative Treatment

If adhesions of small bowel are suspected without complete bowel obstruction and other causes are excluded, the conservative therapy could be initiated. It consists of bowel rest, intravenous fluids, and NG tube placement. In nonpregnant patients, plain abdominal X-ray is indicated every 6–12 h, but in pregnant population, clinical evaluation every 6 h can indicate further diagnostic workup.

7.4.6.2 Surgical Treatment

Emergent exploration is indicated if there is:

- Clinical deterioration
- Unsuccessful conservative therapy (48 h)
- Strangulation suspected initially or during conservative treatment (clinical deterioration, elevation of WBC and CRP)

Total adhesiolysis is always indicated, as in general population, to eliminate the possibility of postoperative bowel kinking around remaining adhesions.

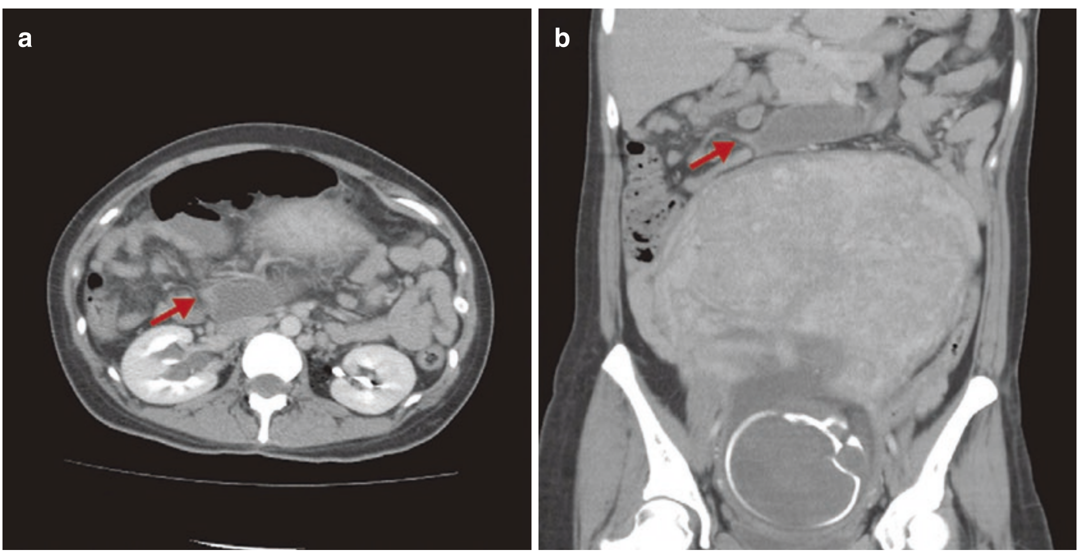

Fig. 7.25 (**a**) Axial view of upper abdominal CT scan. The bird-beak shape indicates the obstructive level of the duodenum-jejunum junction (*red arrow*). (**b**) Coronal view of upper abdominal CT scan. The same bird-beak shape could be identified (*red arrow*). The distended intestine was at the proximal end. Reproduced with permission from [138]

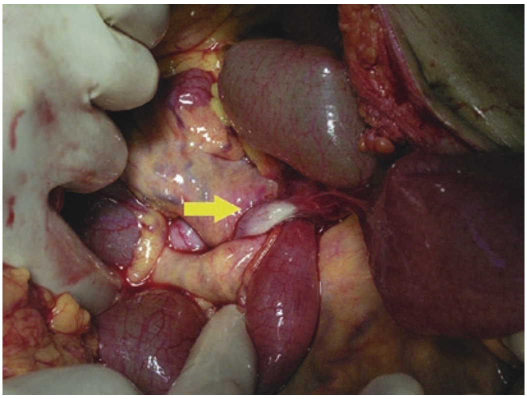

Fig. 7.26 The adhesion band was identified during operation (*yellow arrow*). Above the adhesion band, the distended proximal duodenum was found. Reproduced with permission from [138]

7.5 Small Bowel Volvulus

7.5.1 Small Bowel Volvulus

7.5.1.1 Incidence

Small bowel volvulus is rare in Western countries but common in Africa, India, Nepal, and the Middle East [139–141]. It represents only 1–3% of cases of intestinal obstruction in pregnancy [142]. The major sites of volvulus are the sigmoid colon, the cecum, and the small bowel [143]. Small bowel volvulus especially secondary to malrotation is extremely rare (see Sect. 7.5.2). Most cases of intestinal obstruction secondary to small bowel volvulus occur in the third trimester or puerperium [6, 139, 144–147], but cases in the first trimester were also described [148].

7.5.1.2 Pathophysiology

Primary small bowel volvulus can occur without any predisposing cause. Volvulus is a consequence of the intestine rotating about its mesenteric axis, eventually resulting in a closed-loop obstruction. Conditions implicated in the development of volvulus include adhesions, congenital bands, Meckel's diverticulum, and hernias. It is thought that in advanced pregnancy, the enlarged uterus displaces the mobile cecum out of the pelvis into the right upper quadrant, where the small bowel mesentery and superior mesenteric vessels become the points of rotation and torsion. However, spontaneous detorsion is restricted by the position of the gravid uterus [149, 150]. The uterus enlarges most rapidly between 16 and 20 weeks and again between 32 and 36 weeks, and obstruction occurs most frequently at these times [151, 152]. Volvulus results in partial or complete obstruction of the small intestine with proximal distention and torsion at the point of fixation [5]. Torsion of the small bowel around its mesentery results in obstruction of the mesenteric blood flow, which can then lead to severe ischemia followed by extensive bowel infarction.

7.5.1.3 Clinical Presentation

During pregnancy intestinal volvulus can be extremely difficult to diagnose clinically, as the physical signs can be misleading and may not be those of classic bowel obstruction. Patients typically complain of severe abdominal pain that appears to be out of proportion to the physical signs. Clinical presentation of small bowel volvulus is due to both the mechanical obstruction and the vascular compromise with resultant ischemic bowel. Initial symptoms are similar to those common in pregnancy, including crampy abdominal pain, nausea, vomiting, and constipation, frequently delaying definitive diagnosis. Persistent vomiting may be accompanied by normal or hypoactive bowel sounds. Different from the intermittent, paroxysmal, and regular pain of a uterine contraction, abdominal pain of volvulus is ongoing and mostly epigastric. Feculent vomiting is a sign of a complete bowel obstruction. Classical findings of bowel obstruction in the nonpregnant patient, including constipation, altered bowel sounds, abdominal distention, and peritoneal signs, are frequently obscured by the gravid uterus [143, 151, 152]. When bowel ischemia ensue hematemesis could lead to an initial diagnosis of upper gastrointestinal bleeding [153]. In advanced ischemia with bowel gangrene, signs of peritonism with shock are present.

7.5.1.4 Diagnosis

Transabdominal Ultrasound

Abdominal ultrasonography may give some information about the fetus in addition to ruling out other pathologies. Distended loops of small bowel and free fluid can be detected [154], indicating a small bowel obstruction.

Abdominal CT

Radiological evidences of volvulus on CT scan are (Fig. 7.27) dilated bowel loops, intramural gas (signs of bowel ischemia), thickened bowel wall, twisted root of mesentery, and the “whirlpool” sign [6].

7.5.1.5 Treatment

Resuscitation, including fluid replacement, electrolyte balance correction, prophylactic antibiotics, and nasogastric decompression, is the principal initial treatment. Treatment is always surgical, and type of operation depends on the stage of ischemia caused by volvulus. If the bowel is vital, then the cause of the volvulus is eliminated, and the bowel detorsed to its normal position with the mesentery behind the bowel. The bowel can be ischemic but not necrotic to be detorsed and treated without resection. If the bowel is necrotic, then it should be resected, and the decision of performing the anastomosis is made. If any additional pathology is found that could be the cause of small bowel volvulus, it should be resected and adhesions divided if present. Some of these cases may have extensive bowel infarction, and the consequence of resection is severe short bowel syndrome, which would require long-term total parenteral nutrition [155–157]. If the complete small bowel is necrotic (Fig. 7.28), it is incompatible with survival [147]. If bowel vitality is questionable, it is left in situ and second-look operation after 24–48 h performed [153]. If there are signs of small bowel congestion during the first operations, mesenteric vein thrombosis is likely, as a consequence of mesentery torsion, and the patient should be placed on anticoagulant therapy with i.v. heparin. Subsequently, peroral

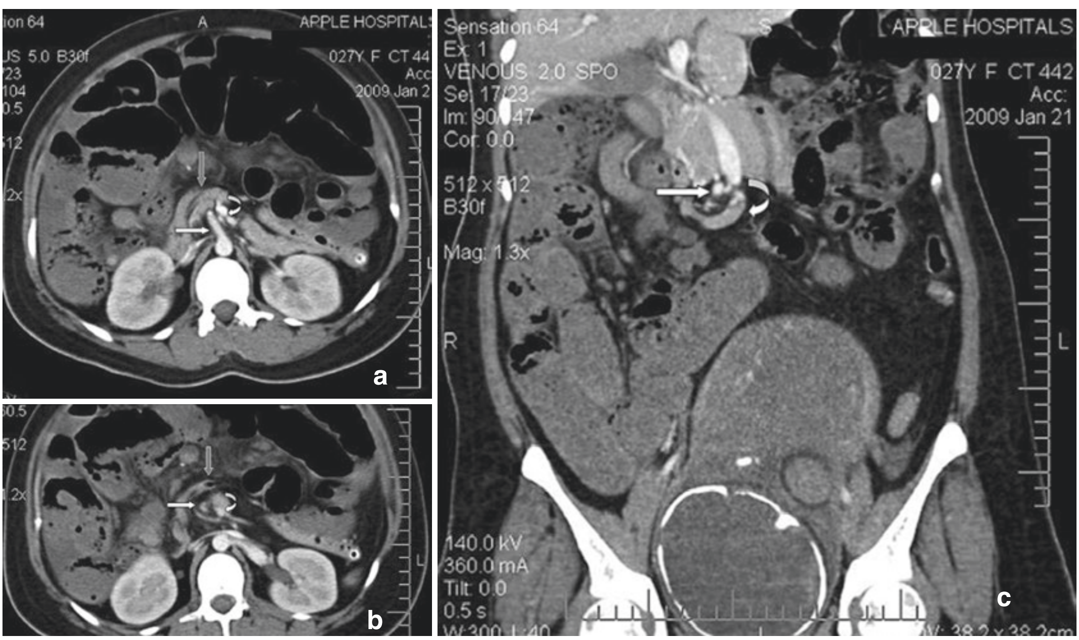

Fig. 7.27 (**a, b**) Axial post-contrast CT scans at the level of the root of small bowel mesentery. Superior mesenteric artery (*white horizontal arrow*), superior mesenteric vein (*curved arrow*), and the twisted root of mesentery and duodenum (*gray vertical arrow*) are shown. (**c**) Coronal reconstruction of redistribution phase shows twisted superior mesenteric vein (*curved arrow*) around the superior mesenteric artery (*horizontal white arrow*). Reproduced with permission from [147]

Fig. 7.28 All small bowel loops congested and infarcted due to volvulus incompatible with survival. Reproduced with permission from [147]

anticoagulants should be introduced for 6 months (target INR of 2.5) [153].

7.5.1.6 Prognosis

Early diagnosis and management are essential to avoid infarction of the bowel. The rate of bowel resection is still high, around 68%, during the last 20 years [146]. The condition may result in a maternal mortality rate of 6–20% and a fetal loss in 22–50%, even with a delay of 24 h [158]. Maternal and fetal mortality is 3–15% and 22%, respectively (another 14% of newborns with proven asphyxia) [146, 147]. These numbers are higher than in general population. Despite medical improvements in all fields, complete small bowel necrosis [147], especially if part of the large bowel is included, is incompatible with survival [159].

7.5.2 Congenital Intestinal Malrotation

7.5.2.1 Incidence

Congenital small bowel malrotation in pregnancy is extremely rare. There are only a few case reports highlighting this condition in gravid patients [142, 149, 150, 160–163].

7.5.2.2 Etiopathogenesis

Patients with malrotation are at an increased risk of presenting with volvulus during pregnancy due to the displacement of bowel loops by the gravid uterus. This is especially true during 16–20 and 32–36 weeks or during puerperium when rapid changes in uterine size occur [149]. Volvulus results in partial obstruction of the small intestine with proximal distention and torsion at the point of fixation [5]. The problem with this entity is that volvulus of the complete small bowel [163] or even a more complex presentation with volvulus of the small intestine, cecum, and ascending colon [161] could ensue with bowel necrosis which is incompatible with life.

7.5.2.3 Clinical Presentation

Malrotation of the midgut rarely presents in adulthood; most present in the neonatal period. When diagnosed in adulthood, it usually remains asymptomatic, with incidental discovery on imaging. Clinical presentation is the same as small bowel volvulus without malrotation (see Sect. 7.5.1.3).

7.5.2.4 Diagnosis

See Sect. 7.5.1.4.

7.5.2.5 Treatment

Due to the possibility of complete small bowel necrosis, emergency laparotomy is indicated if the condition is suspected to prevent bowel necrosis. Surgical resection for volvulus is the preferred treatment, as it eliminates the risk of recurrence [155]. Detorsion has also been suggested as an option if the bowel has not undergone necrosis and ischemia; however, there remains a risk of recurrence. If the obstruction is partial, then prolonged total parenteral nutrition until delivery is an option [164]. After delivery, Ladd's procedure should be performed to eliminate the possibility of midgut volvulus in subsequent pregnancies [164]. There is one case with derotation made with enteroscope with the placement of nasojejunal tube with the endoscopically proven mucosal vitality of duodenum and jejunum. This is not recommended due to several dangerous points. First, there is an increased risk of small bowel perforation during probing of the abruptly short-twisted segment. Second, there is

an increased risk of recurrence due to the possibility of only partial derotation [142]. If gangrene of small bowel is present (Fig. 7.29), treatment algorithm is the same for bowel necrosis of any cause (see Sect. 7.5.1.5).

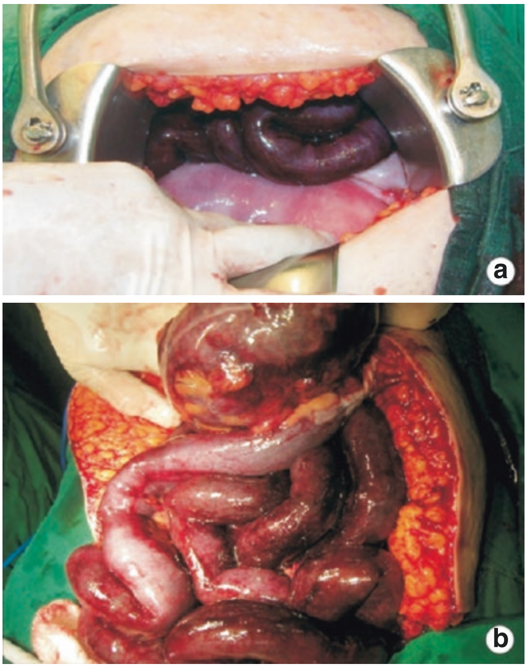

Fig. 7.29 (**a**) Small intestine with the ischemic change above the uterus. (**b**) The ischemic intestine due to volvulus from the proximal transverse colon, with the ischemic portion extending toward to Treitz's ligament of the small intestine. The ischemic ascending colon was located in the middle of the peritoneal cavity. Reproduced with permission from [159]

7.5.2.6 Prognosis

Prognosis depends on the severity of bowel ischemia and length of bowel seized with ischemia (see Sect. 7.5.1.6).

7.5.3 Ileosigmoid Knotting

7.5.3.1 Definition

The specific type of small bowel volvulus or sigmoid volvulus is *ileosigmoid knotting* (ISK), classified into four types by Alver et al. in 1993. Type I (Fig. 7.30) is the most common one and occurs when the ileum (active component) revolves around the sigmoid colon. In Type II, the sigmoid colon (active component) revolves around the ileum. In Type III, the ileocecal portion revolves around the sigmoid colon. When it is difficult to determine the active or passive component, it remains undetermined or indefinite type (Type IV). Type I and II can be classified into subtypes of A and B depending on whether the torsion is clockwise or counterclockwise, respectively [165]. The first report in general population was by Parker in 1845, and Dunkerley reported the first case in the general population from India in 1953.

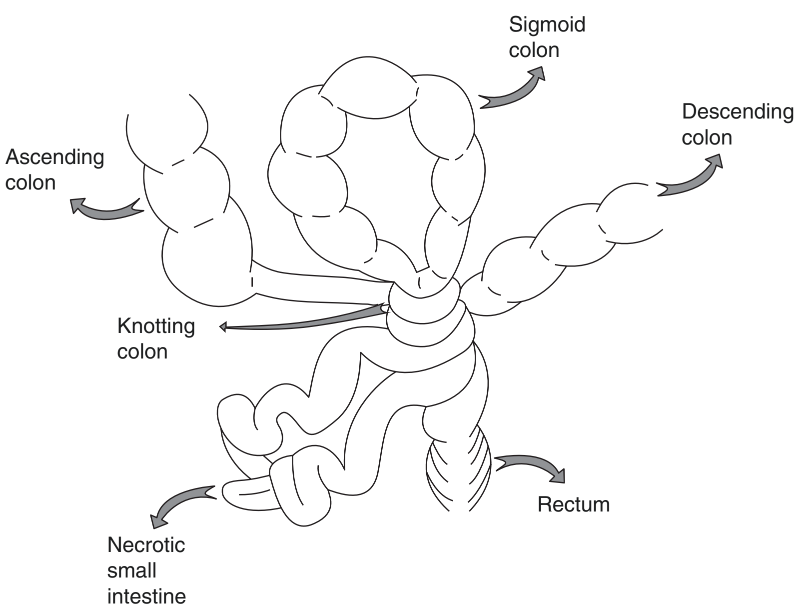

Fig. 7.30 Ileal knotting type I. Reproduced with permission from [166]

7.5.3.2 Incidence

ISK as a specific cause of small bowel volvulus and intestinal obstruction in pregnancy was present in only 15 cases between 1951 and 2014 [166–173], with an incidence ranging 3.2–5.9% of all ISK cases and 12.5–36.4% of cases in female patients [165, 168, 174]. All patients were multiparous and almost all (11/12) in the third trimester [169], with wide age distribution. It is probably underreported partly due to the published cases under other terms such as compound volvulus before the term ISK was coined by Shepherd in 1967 [175]. Studies in developing countries showed that ISK accounts for 15–17% of the cases of sigmoid volvulus in general population [176–178].

7.5.3.3 Etiopathogenesis

Patients with ISK, as in other forms of small bowel volvulus during pregnancy, are at an increased risk during pregnancy due to the displacement of bowel loops by the gravid uterus. This is especially true during 16–20 and 32–36 weeks or during puerperium when rapid changes in uterine size occur [149]. The problem with this entity is that volvulus of the complete small bowel [163] or even a more complex presentation with volvulus of the small intestine, cecum, and ascending colon [161] could ensue with bowel necrosis which is incompatible with life.

Another mechanism is when a semifluid, bulky meal progresses into the proximal jejunum, it increases the mobility of the intestine, and the heavier segments of the proximal jejunum fall into the left lower quadrant. The empty loops of the ileum and distal jejunum twist in a clockwise rotation around the base of a narrow sigmoid colon. Further peristalsis forms an ISK with two closed-loop obstructions—one in the small bowel and the other in the sigmoid colon [168]. Both the ileal loops and the sigmoid colon become distended. As the knot tightens, a double loop obstruction may progress to gangrene. The presence of an elongated ileum and sigmoid colon and the presence of a narrow base with an elongated mesentery have been held responsible for the anatomical pathology of the disease. It has been suggested that the rapid shrinking of the uterus after delivery and sudden changes in the position of the abdominal organs might induce this condition. Sometimes it cannot be established whether ileal knotting triggered labor or labor triggered ileal knotting and the ensuing events [166]. All known risk factors are presented in Table 7.6.

7.5.3.4 Clinical Presentation

The typical triad of ISK is intermittent abdominal pain progressing to constant pain increasing in severity, asymmetrical abdominal distention (Fig. 7.31), and absolute obstipation [169]. Additional symptoms may include nausea and

Table 7.6 Risk factors for ileosigmoid knotting in pregnancy

Bulky single daily meal
Eating habit
Ramadan fast
Morning sickness
Anatomic factors
Long small bowel mesentery
Hypermobile small bowel
Long sigmoid colon on a narrow pedicle
Relaxed anterior abdominal wall
Pregnancy
Multiparous
32–36 weeks
Puerperium
Adhesions
Meckel's diverticulum
Internal herniations
Bowel malrotation

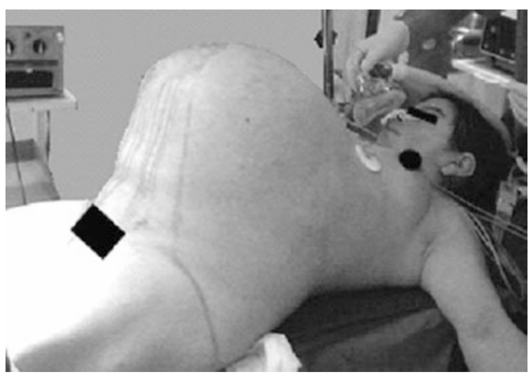

Fig. 7.31 Asymmetrically, atypically distended abdomen appeared after delivery and again at puerperium. Reproduced with permission from [166]

vomiting, and other signs may include hyperkinetic or hypo/akinetic bowel sounds, empty rectum, fever, and dehydration. Muscular guarding with rebound tenderness and melena are suggestive of peritonitis and/or bowel gangrene. The clinical appearance of ISK in pregnant women is not distinctive from the presentation in nonpregnant females [169, 174]. The mean duration of symptoms is shorter for the pregnant women than for the nonpregnant female patients, but the difference is not statistically significant (36.0 vs. 46.8 h) [169].

7.5.3.5 Diagnosis

The accuracy of preoperative diagnosis of ISK in pregnancy is 14% (last seven published cases) due to its infrequency and atypical radiographic findings [173]. Preoperative diagnosis in pregnant patients is usually nonspecific intestinal obstruction.

Plain Abdominal X-Ray

The key radiological features on plain abdominal X-rays of ISK consist of a dilated loop of the sigmoid colon, evidence of small intestinal obstruction, and retention of feces in an undistended proximal colon (Fig. 7.32). The dilated loop usually lies on the right side of the abdomen, and the limbs taper inferiorly into the right lower quadrant. Medial deviation of the distal descending colon is an inconsistent but highly specific finding [179]. Probably these classic findings are not commonly present during pregnancy due to the distorted anatomy especially in advanced pregnancy when ISK is more common.

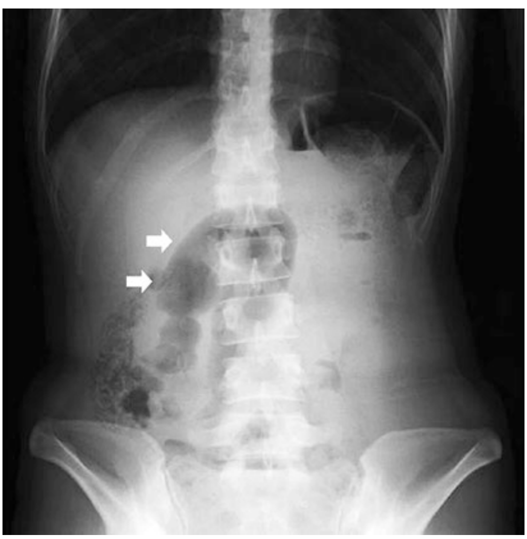

Fig. 7.32 Plain abdominal X-ray reveals a sigmoid colon loop (*white arrows*) in the mid-abdomen with air–liquid levels of small bowel around sigmoid colon base. Reproduced with permission from [173]

Transabdominal Ultrasound

Abdominal ultrasonography may give some information about the fetus in addition to ruling out other pathologies. Distended loops with thickened bowel wall are visualized. Further diagnosis information with ultrasound is rarely informative.

Abdominal CT

Despite its high diagnostic rate in general population [180, 181], abdominal CT is rarely used. Abdominal CT demonstrates a twisted and dilated sigmoid colon with whirled sigmoid mesentery, in addition to twisted and dilated small intestinal segments (Figs. 7.33 and 7.34).

Abdominal MRI

In contrast to rarely performed abdominal CT scan, abdominal MRI may be helpful in selected cases [182].

7.5.3.6 Treatment

Due to the possibility of complete small bowel necrosis, emergency laparotomy is indicated if

Fig. 7.33 Contrast-enhanced CT (*axial view*) shows a dilated loop of intestine with a surrounding whirl (*white arrows*). Reproduced with permission from [173]

Fig. 7.34 Contrast-enhanced CT (*coronal view*) shows a dilated loop of the sigmoid colon in the right lower abdomen with whirling of the sigmoid mesocolon and mesenteric root, suggestive of strangulation. Dilated loops of small bowel are concentrated in upper left abdomen. Reproduced with permission from [173]

the condition is suspected to prevent bowel necrosis. Surgical resection for volvulus is the preferred treatment [155]. If small intestine and sigmoid colon are gangrenous, then ileal resection with primary anastomosis and sigmoid resection with Hartmann's procedure is performed. If the only ileum is gangrenous, it is resected and primary anastomosis made. Due to the high incidence of recurrent (isolated) sigmoid volvulus (in both general and pregnant population) [155, 183, 184], it should be resected even if vital and Hartmann's procedure performed (see Sect. 7.8.5).

Detorsion (with sigmoidostomy or sigmoidopexy) is an option if the bowel has not undergone necrosis and ischemia; however, there remains a risk of recurrence. It is used to shorten the operation in an unstable patient. Because untwisting the knot is both difficult and risks toxin release and perforation, it has been advised that the sigmoid colon is deflated by means of needle deflation or colotomy or en bloc resection of the gangrenous colon.

If the obstruction is partial, then prolonged total parenteral nutrition until delivery is an option [164]. After delivery, Ladd's procedure should be performed to eliminate the possibility of midgut volvulus in subsequent pregnancies [164]. There is one case with derotation made with enteroscope with the placement of nasojejunal tube with the endoscopically proven mucosal vitality of duodenum and jejunum. This is not recommended due to several dangerous points. First, there is an increased risk of small bowel perforation during probing of the abruptly short-twisted segment. Second, there is an increased risk of recurrence due to the possibility of only partial derotation [142].

7.5.3.7 Prognosis

In general population, the mean mortality rate of ISK is 6.8–8% with nongangrenous and 20–100% with gangrenous bowel [182]. Although the mortality and morbidity rates when ISK was the cause of small bowel volvulus were higher in the pregnant patients, the differences were not statistically significant (33.3% vs. 18.8%). The mean hospitalization period was longer for the pregnant patients than for the nonpregnant female patients (15.5 vs. 10.8 days) [169]. Mortality covering last seven published cases was 57% [173].

7.6 Carcinoma of the Colon and Rectum

7.6.1 Historical Perspective

Cruveilhier reported the first case of rectal carcinoma in pregnancy in 1842 [185]. The first case of colon cancer above peritoneal reflection was reported by Evers in 1928 [186].

7.6.2 Incidence

Only 2–6% of CRC is found before the age of 40 which is a period of reproductive age [187]. However, CRC presenting in pregnancy is an uncommon disease with a reported incidence 0.002–0.1% [187–191]. Nijhoff (Groningen, Netherlands), in 1905, collected 22 published cases [192]. Up to 1993, another 25 cases were published [74]. Review from 1993 included 41 cases with following tumor distribution: right

colon (7.3%), transverse colon (4.9%), left colon (4.9%), sigmoid colon (19.5%), and rectum (63%). Dukes' stage at presentation was A, 0%; B, 39%; C, 41%; and D, 15% (two patients unstaged) [193]. Up to 2005, there have been over 275 published cases [193–195]. In the biggest study of 134 patients, 76.8% were diagnosed postpartum whereas only 20.9% before delivery and 2.2% at delivery [189].

> Pregnant women have a much higher incidence of rectal cancer (83%), compared with colon sites (17%). This is in contrast to nonpregnant women younger than 40 years, among whom the site distribution is 68% colon and 32% rectum, respectively [196].

7.6.3 Carcinogenesis and Risk Factors

7.6.3.1 Hormonal Receptors

Estrogen receptors (ER) and progesterone receptors (PgR) [197] may be involved in the pathogenesis of CRC during pregnancy. As many as 20–54% of colon tumors have ERs [198] and as many as 42.8% of colon tumors have PgRs [199]. These findings suggest that increased levels of estrogen and progesterone found in pregnant women could stimulate the growth of CRCs that have these receptors. Stimulation of these receptors could also help to explain the advanced stages found in the majority of patients at the time of diagnosis. However, the data to support the role of these receptors in the pathogenesis of CRC are scarce and that conflicting data exist regarding ERs and PgRs in CRC. One study claims that there are no ER+ and almost no PgR+ (1/156) tumors in women diagnosed with CRC [198].

7.6.3.2 COX-2 Enzymes

The role of COX-2 enzymes in CRC and pregnancy has also been studied. COX-2 products appear to be essential for the early sequences of pregnancy, including ovulation, fertilization, implantation, and decidualization [200]. The early events of pregnancy and the pathogenesis of tumor spread have important similarities: both events require cells to migrate from the site of origin to another site at which these cells must establish new vasculature to grow and mature [200]. COX-2 enzymes are found in high levels in many CRC cells [201]. COX-2 inhibitors such as aspirin can alter the course of CRC [201]. Increased levels of COX-2 enzymes in pregnant patients could play a role in the pathogenesis and prognosis of CRC in pregnancy. However, no studies have been performed to explore this potential relationship [194].

7.6.3.3 Other

CRC is a rare event in young patients. This implies that CRC in pregnancy among this population of patients is likely caused by the presence of predisposing factors compared with the general population of patients with CRC.

Parity is neither positively or negatively associated with CRC [189].

Increasing age is associated with an increased risk for the development of CRC, with a small number of cases in women less than 30 years old [190, 202, 203].

Predisposing factors for CRC include hereditary nonpolyposis CRC (i.e., Lynch syndrome), familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, and prolonged history of inflammatory bowel disease [194]. However, these increased risk groups represent only a small portion of CRCs diagnosed in pregnancy [195]; around 21% of pregnant patients with CRC had one of these strong predisposing factors for CRC [191]. The presence of genetic abnormalities is not known. A family history must be recorded in all patients, and an evaluation by cancer genetic clinics should be considered [194].

In countries fortifying flour with folic acid, a steady decrease in the incidence of neural tube defects (NTDs) has been documented [204]. The main criticism against flour fortification has been that this strategy exposes large segments of the population, such as those who never become pregnant, to levels of folate beyond what may be necessary [205]. In parallel to the reports on a dramatic decrease in rates of NTDs in

jurisdictions where fortification took place, concerns have been raised that heightened folate status may increase the risk of cancer in general, with CRC on the top [206]. High folate level decreases the risk of CRC between 8–15% [207] and 19–25% [208]. Women of reproductive age should not be discouraged from an adequate intake of folate based on a wrongly perceived risk of CRC.

7.6.4 Clinical Presentation

7.6.4.1 Elective Presentation

The most common clinical manifestations of CRC include nonspecific, vague abdominal pain, nausea, vomiting, weight loss, change and irregularity in bowel habits, and rectal bleeding. Some of these symptoms are commonly found in pregnant patients and are usually considered to be the usual manifestations of pregnancy, without an appropriate evaluation [194, 209]. The delay in initiating the workup for the symptoms related to CRC is one of the major contributing factors to the poor prognosis [210]. In general, pregnant women gain weight. However, women can experience weight loss in the first trimester due to nausea and hyperemesis gravidarum. On the other hand, pregnancy can obscure weight loss secondary to CRC in second and third trimesters. Rectal bleeding is a common finding during pregnancy and is usually secondary to the high incidence of both external and internal hemorrhoids; however, rectal bleeding is a particularly ominous sign and should never be attributed solely to pregnancy itself without a proper evaluation. It is highly suspicious if the fresh blood is mixed with stool if a large amount of mucus is present, an old blood is found of if unexplained diarrhea, with or without blood is evident. Digital rectal examination with anoscopy is mandatory in every patient with these symptoms. Nausea and vomiting are very common symptoms of pregnancy, particularly during the first trimester. Constipation often accompanies pregnancy, which, again, can delay workup for CRC. Abdominal mass constitutes a natural process in pregnancy. Potential palpable masses secondary to CRC are often missed especially in advanced pregnancy. The patient with Krukenberg tumor from primary CRC can present with virilization—facial hirsutism, deepening voice, facial acne, and clitoromegaly [211].

7.6.4.2 Emergent Presentation

Emergent presentation due to CRC obstruction is somewhat easier to diagnose on clinical grounds. Profound vomiting, sometimes feculent, is a signal of bowel obstruction. Patients have severe abdominal pain which is colicky at the beginning and then constant with significant abdominal distention during the short period despite the trimester of pregnancy. There is an absence of stool and more importantly flatus.

7.6.5 Differential Diagnosis

In the early pregnancy, a bowel obstruction can initially be confused with hyperemesis gravidarum. The difference is found during examination of the abdomen. When large bowel obstruction is present without competent ileocecal valve, feculent vomiting is present with significant distention of the abdomen. There is no passage of flatus and stool, while bowel habits during hyperemesis gravidarum are normal. Sometimes, in advanced pregnancy, clinical presentation is attributed to threatened labor [212]. Diagnostic delay in a patient with virilization due to Krukenberg tumor is more pronounced if the patient had prepregnancy diagnosis of polycystic ovary syndrome [211]. New onset virilization, especially with other symptoms, such as (new onset) obstipation or (new onset) rectal bleeding, should raise suspicion of CRC. The list of differential diagnoses is presented in Table 7.7.

Table 7.7 Differential diagnoses and causes of colorectal obstruction in pregnancy

Differential diagnosis	Cause of obstruction
Hyperemesis gravidarum	Endometriosis
Gastroenteritis	Adhesions
Threatened labor	Volvulus
Constipation	Intussusception
Mesenteric ischemia	

7.6.6 Diagnosis

7.6.6.1 Laboratory Findings

The serum carcinoembryonic antigen (CEA) levels are normal or marginally elevated in a normal pregnancy [195, 209]. The CEA levels should, therefore, be measured and used in the same way as in nonpregnant patients [209]. Although the CEA level is not useful as a screening test for CRC because of its low sensitivity and low specificity, preoperative testing is useful in determining the prognosis and for providing a baseline for comparison with postoperative levels. Anemia is a physiological finding in pregnancy; therefore, lower hemoglobin levels are not diagnostic, but microcytic anemia or low iron levels should raise suspicion of bleeding, not the dilution of pregnancy [212]. In such cases fecal occult blood test is mandatory.

7.6.6.2 Plain Abdominal X-Ray

The use of diagnostic imaging modalities differs between the elective and emergent presentation of CRC in pregnancy. In the emergent presentation, plain abdominal X-ray is sufficient for the diagnosis of the colorectal level of obstruction. In the elective presentation, there is no diagnostic value of plain abdominal X-ray.

7.6.6.3 Transabdominal Ultrasound

Abdominal ultrasound rarely defines primary CRC but can show liver metastases as an indirect clue to the diagnosis. Ovarian metastatic disease from CRC poses another diagnostic challenge. The incidence of ovarian metastases from CRC (Krukenberg tumor) is higher in pregnant (25%) than in nonpregnant (3–8%) patients [210, 213]. It could mislead the clinician to make the diagnosis of primary ovarian tumor preoperatively (Fig. 7.35) with a false diagnosis of external colon compression from ovarian tumors.

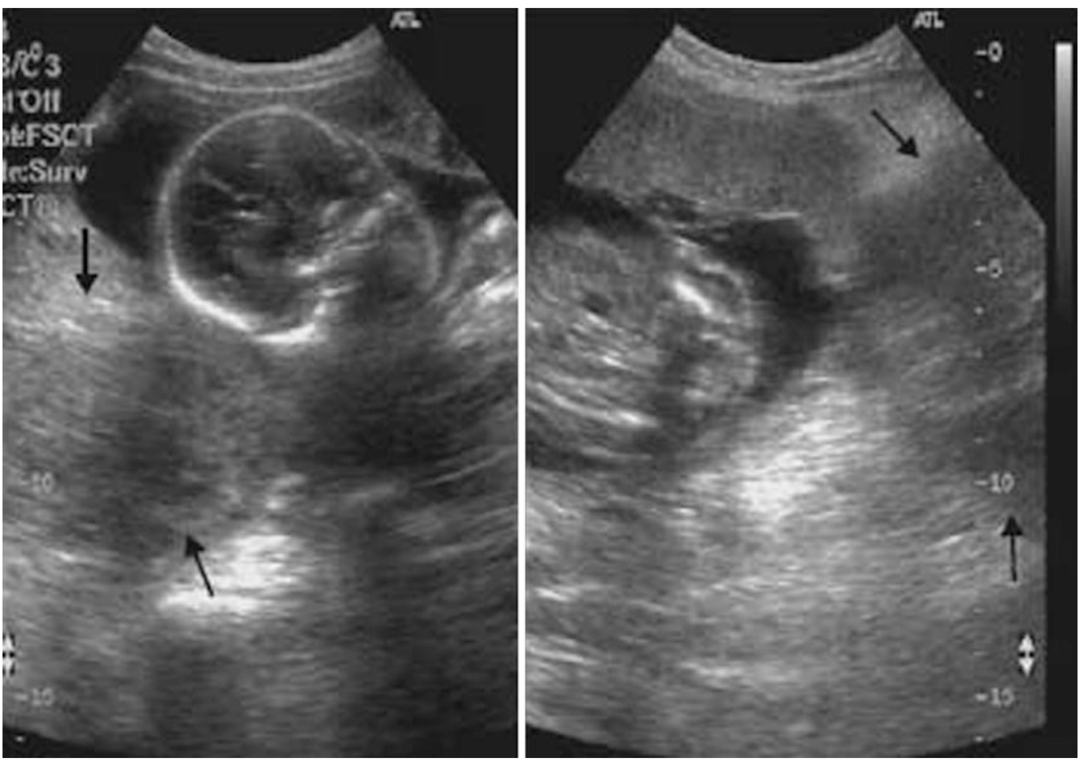

Fig. 7.35 Ultrasonogram showing the fetus and two ovarian masses (*black arrows*). Reproduced with permission from [214]

Fig. 7.36 Pretreatment T2-weighted sagittal view MRI of the pelvis showing thickening involving anorectum 1.2 cm from anal verge and extending 4.2 cm craniocaudally. Uterus is anteverted and shows gestational sac. Reproduced with permission from [215]

7.6.6.4 Abdominal MRI

MRI is the most accurate diagnostic imaging modality for CRC in pregnancy. It accurately defines the location and an extent of a rectal carcinoma (Fig. 7.36). Also, metastatic CRC in a form of a Krukenberg tumor can be delineated (Fig. 7.37). Hepatic metastases, the most common metastatic disease of CRC, are common with Krukenberg tumor during pregnancy (Fig. 7.38).

7.6.7 Treatment

7.6.7.1 Surgical Treatment

Nijhoff in 1905 held that as the child is not viable, the operator must choose between terminating the pregnancy and waiting until the child is viable. He advocated the former procedure, believing that by waiting for an operable tumor might be allowed to become inoperable [192].

After 20 weeks of pregnancy, it is recommended that surgery is delayed to have a reasonable maturation of the fetus. When CRC is diagnosed after 32 weeks, CS is recommended after documentation or stimulation of fetal lung maturity with concomitant tumor resection [189, 190]. CRC surgery can be done right after an uncomplicated CS [209].

Fig. 7.37 MRI of the pelvis (T2 weighted) showing metastatic left ovarian tumor at 23 weeks of gestation from the primary carcinoma of the sigmoid colon. Reproduced with permission from [213]

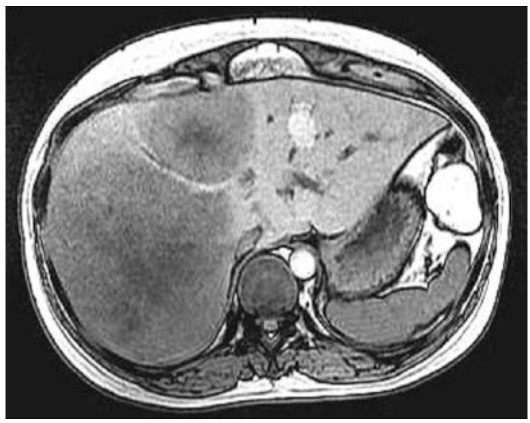

Fig. 7.38 MRI of the liver (T1 weighted) showing liver metastases from the primary sigmoid carcinoma of the same patient in the Fig. 7.37. Reproduced with permission from [213]

If the operation is performed without termination of pregnancy, the patient should be placed in the slight left lateral position to prevent uterine compression of the inferior vena cava and left iliac vein. Maternal blood gases should be monitored, as CO_2 insufflation can induce maternal hypercapnia, which can lead to fetal hypercapnia, tachycardia, and hypertension.

When faced with malignant bilateral ovarian tumors, the ideal surgical approach is total hysterectomy, bilateral salpingo-oophorectomy, pelvic and abdominal washings, omentectomy, and para-aortic lymph node biopsies. However, even in the event of bilateral malignant disease, it is possible to omit hysterectomy if the uterus is not grossly involved, thus allowing the preservation of an existing pregnancy. Macroscopic ovarian metastases from primary CRC are present in 3.4–5.4% in general population [216]. Currently, there are no guidelines for the role of prophylactic oophorectomy in the prevention of metachronous ovarian metastases. Surgical and adjuvant treatments have obvious implications for women of childbearing age.

7.6.7.2 Conservative and Bridge Therapy

Along with surgery, other approaches to bowel obstruction can be considered. Retrograde insertion of a colonic stent in general population has been widely used for the relief of a colonic obstruction caused by malignancy [210]. Colonic stent decompression can provide palliation in patients with the widespread metastatic disease or serve as a bridge to surgery but at the risk of greatly increased maternal and fetal morbidity [6].

7.6.7.3 Mode of Delivery

The mode of delivery should not be affected by cancer, with the exception of a CS owing to a distal tumor obstructing the birth canal or anterior rectal wall carcinoma. Unfortunately, pregnancy-associated cases of CRC have higher rates of CSs and preterm deliveries. Preterm deliveries are not only secondary to scheduled inductions and CSs related to the woman's cancer diagnosis but also to higher rates of preterm labor [189]. The placenta should be carefully examined for metastases [210].

7.6.7.4 Chemotherapy

Adjuvant chemotherapy with *5-fluorouracil* (5-FU) is suggested for stage III CRC; however, the risk and benefits should be discussed with the patient [209]. The most serious complications occur when the chemotherapy is given during 3–12 weeks of gestation [217]. Mechanisms by which 5-FU may lead to fetal abnormalities include interrupting DNA synthesis and cell development through inhibition of embryonic thymidylate synthase [218]. During the first trimester, 5-FU has been associated with spontaneous abortion as well as normal-term births [219, 220]. Moreover, no congenital anomalies or other clinically significant adverse effects were observed in infants whose mothers were treated for breast cancer during the second and third trimesters of pregnancy with intravenous 5-FU in combination with doxorubicin, cyclophosphamide, and other chemotherapeutic agents [221]. There are no reports on the use of 5-FU during lactation.

Cisplatin and other platinum-based chemotherapy drugs are also used in CRC, but they are not recommended during pregnancy or breastfeeding [222]. Studies in animals have shown that oxaliplatin causes miscarriages, decreased weight or death of the fetus, and problems with bone formation [223]. Patients should use some kind of birth control while receiving oxaliplatin, and a pregnancy test should be performed before initiation of chemotherapy. Some recommend lower doses of chemotherapy during pregnancy because of higher concentration of the free chemotherapeutic agent in pregnant woman compared with nonpregnant women [224]. In addition to the dose reduction, within 3 weeks of anticipated delivery or beyond 35 weeks of gestation, it should not be administered to avoid transient neonatal myelosuppression and potential complications such as bleeding, sepsis, and death at the time of delivery [225]. In five published studies consisting of 11 patients treated with combination chemotherapy including cisplatin for cervical cancer in pregnancy, neonatal

development was normal [226]. It is not known whether this drug passes into breast milk.

Irinotecan was approved as part of a first-line treatment regimen containing 5-FU and leucovorin for metastatic CRC. It resulted in significant improvements in objective tumor response rates, time to tumor progression, and survival when compared with 5-FU and leucovorin alone [227]. Irinotecan is a US FDA pregnancy class D drug, meaning that human data show risk but the potential benefit may outweigh the risk. It may cause harm to the fetus when given during pregnancy [228]. Radiolabeling studies have shown that 14C-irinotecan crosses the placenta of rats after intravenous administration. Administration of irinotecan to rats during the period of organogenesis is embryotoxic as characterized by increased postimplantation loss and decreased numbers of live fetuses. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to pregnant rats after the period of organogenesis through weaning caused decreased learning ability and decreased female body weights in the offspring. Irinotecan is excreted into breast milk, and breastfeeding is not recommended during therapy. The mean terminal elimination half-life for its longest-acting active metabolite, 7-ethyl-10-hydroxycamptothecin, is 10–20 h, meaning that breastfeeding should be safe after at least 1 week off treatment. There are two case reports with irinotecan (plus 5-FU and leucovorin) use. One in 18 weeks of pregnancy and the other in 23 weeks of pregnancy without any harmful effect on the neonate/infant [229, 230].

Chemotherapy is safer during the second and third trimester of pregnancy, although there is an increased incidence of intrauterine growth retardation and prematurity [231]. Fetal growth could also be affected by maternal nutritional deficiencies and anorexia induced both by chemotherapy and the tumor itself [222]. Although a few cancer chemotherapy studies have failed to show adverse effects in treatment in the third trimester, the possible neurocognitive effect of chemotherapy cannot be totally excluded because brain development is not completed during pregnancy or even early in life [232]. Most evidence indicates that neoadjuvant chemotherapy in pregnant women with metastatic rectal cancer spares the fetus, although it is not curative for mothers [233–237].

7.6.7.5 Radiotherapy

Adjuvant radiotherapy is used in the management of rectal cancer. Radiotherapy to the pelvis is not recommended during pregnancy and contraindicated during organogenesis because it is associated with embryonic or fetal death, malformation, and growth retardation [238]. Fetal radiation exposure should be measured by a medical physicist in any radiation during pregnancy [239]. Women with pregnancy-associated CRC were less likely to receive chemotherapy but more likely to receive radiation than aged-matched, nonpregnant women, though the differences in rates of adjuvant radiotherapy were not statistically significant [189]. Because most women were diagnosed after delivery, this phenomenon cannot be fully explained by a concern for the fetus, unless it represents a breastfeeding concern. Future fertility should be considered before proceeding with treatment because radiotherapy can cause permanent damage to ovaries and lead to infertility [240]. If a woman of childbearing age is considering radiotherapy, she must be informed of this possible outcome, and consent must be documented. There are no studies elaborating the timing of radiation and chemotherapy relative to surgery, and so no conclusions can be made.

7.6.8 Prognosis

7.6.8.1 Maternal Outcome

Around 1900 it was stated that permanent hyperemia, the severe relaxation of the tissues, favor a rapid spread of the process to a very great extent, and so an intense aggravation occurs as a rule far more quickly than in the absence of pregnancy. Some claim that this may be attributed to a number of factors: (1) masking of symptoms related to tumor development, as a result of gestation; (2) proliferation and decreased apoptosis of tumor cells due to the effects of various cytokines and hormonal environmental stimuli

related to the state of pregnancy; and (3) the possible state of tolerance to tumor cells acquired in pregnancy as shown to occur in the paternal alloantigens [241].

Prognosis in CRC is largely based on the stage at diagnosis. Pregnant women with CRC are diagnosed at a more advanced stage [193] secondary to delay in diagnosis, and this leads a worse prognosis [242]. It is hypothesized that the development of CRC during pregnancy can be attributed to alterations of the p53 tumor suppressor gene or gene product on one hand and a maternal immune-tolerant state on the other [243]. In a review of 42 patients with CRC above the peritoneal reflection, 56% of patients died by the time the cases were reported. Most died within 1 year of being diagnosed, and the median survival for the group was less than 5 months [244]. One of the possible explanations is a higher percentage of primary signet-ring cell carcinoma which is a rare variant of colorectal adenocarcinomas. The incidence ranges 0.1–0.9% [245]. Microsatellite instability is present in approximately 30% of tumors [56]. This variant of CRC is usually diagnosed at an advanced stage, and patients are usually younger, more likely to experience lymph node metastasis, and have an aggressive clinical course and poor prognosis [215]. The stage at initial diagnosis in women with pregnancy-associated CRC is no different than the aged-matched, nonpregnant population of women with CRC, with a similar distribution of histological subtypes [190, 193, 242]. This is partly due to the similar histologic subtypes between the two populations of women [189] despite some claiming that pregnant women have higher rates of an aggressive, mucinous subtype [242]. Ultimately, survival was no different among women with pregnancy-associated CRC and nonpregnant women with CRC (Fig. 7.39). No data are available for obstruction CRC in pregnancy because it is an extremely rare condition. Large bowel cancer coexistent with pregnancy presents in a distal distribution (64–86% were located in the rectum) and presents at an advanced stage (60% were Dukes C stage or more advanced at the time of diagnosis).

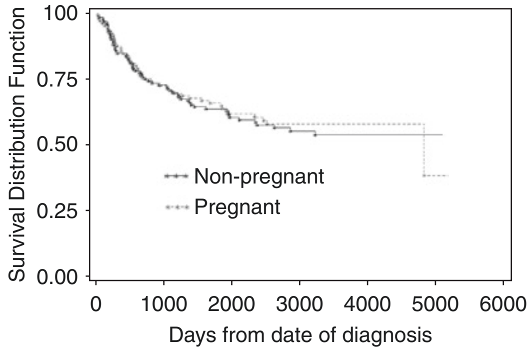

Fig. 7.39 Kaplan–Meier survival distribution for pregnant and nonpregnant women with colon cancer (aged-matched, with similar distribution of histological subtypes) in California, USA, 1991–1999. Reproduced with permission from [189]

Although differences exist between the biology and clinical behavior of anal and colon cancers, all were analyzed together. A separate analysis done after omission of patients with anal cancer yielded perinatal and cancer outcomes virtually identical to those of the group as a whole [189].

The survival of patients in general population, with metastasis involvement of the ovaries, is poor, in the range of 3–12 months [210]. In general population, oophorectomy prolongs survival in patients with ovarian metastases by almost 10 months [246]. There are no data for pregnant population. Some recommend prophylactic bilateral salpingo-oophorectomy simultaneous with CRC surgery [247, 248], while others did not find the incidence of synchronous and metachronous ovarian tumors to be high and overall long-term survival was unaffected [216, 249]. However, it is prudent to take into consideration the desire of the patient for future pregnancies. Also, bilateral salpingo-oophorectomy at the time of resection has been linked to an increased incidence of spontaneous abortion, especially if performed during the first trimester [210]. Another option is obtaining bilateral wedge biopsies of the ovaries during surgery for pathologic examination of the frozen sections with subsequent removal if the ovaries are involved [210].

Obstetrical outcomes were good overall, though pregnancy-associated cases of CRC did

have higher rates of CSs and preterm deliveries. Pregnant women with CRC had a larger number of major puerperal infections. It is possible that women with CRC are more prone to infections that may be subclinical before delivery but predispose them to have preterm labor. This could be secondary to malignancy-related immune suppression or some other unknown cause [189]. Another explanation is that CRC initiates an inflammatory reaction that then starts the preterm labor cascade secondary to the close proximity to the uterus.

7.6.8.2 Fetal Outcome

There are no reports of adverse fetal outcomes due to the CRC itself, even in widespread metastatic disease [250]. Despite the higher rates of preterm delivery, neonatal outcomes are excellent [187, 189, 203, 242]. The rate of infant survival in pregnancies complicated with CRC is reported to be 78.1% [251]. Metastasis to the placenta was reported [252].

> Although a complete evaluation of the placenta is recommended, there is no evidence to support periodic follow-up of the baby. Metastasis of CRC to the products of conception has not been described [202].

7.7 Intestinal Stomal Obstruction

Stoma-related problems occur in half of the patients [253], 68% during the second and third trimester. However, these problems are corrected without medical intervention [254]. For example, the enlarging uterus may drag on the ileostomy loop from within, causing stomal retraction. In one study, 10% of patients with ileostomies had an intestinal obstruction during pregnancy [21].

Various causes of local, intestinal stomal obstruction occur in general population, with an additional contributing factor in pregnancy (Table 7.8). These causes are extremely rare in pregnant patients due to the rarity of stomas in this population and because most of these stomas are temporary. If the patient had stoma before pregnancy, it should be stressed that during pregnancy normal, functional stoma can enlarge and be at least 20 mm bigger (double) than it was prior to pregnancy. This is common and not the sign of ileostomy obstruction or a (incarcerated) parastomal hernia. If the stoma functions normally and the patient is without symptoms, the patient can be reassured, and no diagnostic workup is necessary.

Table 7.8 Causes of intestinal stomal obstruction in pregnancy

Stomal prolapse
Stomal intussusception
Stomal stenosis
Surrounding tumor progression
Parastomal hernia
Adjacent adhesions and kinking
Compression from gravid uterus

Table 7.9 Primary diagnosis for ostomy

Disease	Percent
Ulcerative colitis	63.6
Crohn's disease	15.2
Malignancy	4.6
Bowel injury	1.5
Rectovaginal fistula	1.5
Small urinary bladder	1.5
Polyposis coli	1.5
Unspecified	10.6

Reproduced with permission from [253]

An extremely small number of patients have intestinal stoma during pregnancy, almost all due to inflammatory bowel disease (Table 7.9). These data refer to the presence of ostomy during pregnancy, not to the creation of the soma during pregnancy.

7.7.1 Intussusception and Prolapse

7.7.1.1 Incidence

Intussusception in stoma is extremely rare, and since 1950, more than half (57%) presented during pregnancy [255–257] along with one colostomy intussusception [10].

7.7.1.2 Risk Factors

Pregnancy is a risk factor for stomal intussusception because more than 50% of all ileostomy

intussusceptions are found during pregnancy. There are too few cases for analysis, but in most of the cases, ulcerative colitis was the underlying disease [255–257]. It is a question whether the ulcerative colitis is the cause or most patients with inflammatory bowel diseases have the ileostomy in this reproductive age range. In general population, all factors causing increased intra-abdominal pressure are risk factors for stomal prolapse. Active inflammatory bowel disease causes mucosal edema which can be a promoting factor for intussusception, as well as a stomal prolapse. Corticosteroid therapy can also promote intussusception/prolapse due to wound healing/fibrous tissue processes. In most cases ileostomy was the location of intussusception, which was done before pregnancy [255–257].

7.7.1.3 Clinical Presentation

Clinical presentation of intestinal obstruction is the same as for any other cause (see Sect. 7.1). Clinical diagnosis is somewhat easier because most patients seek medical attention when stoma prolapses and it is commonly before other symptoms develop. Stomal prolapse is rarely accompanied with stomal obstruction (incarceration) or strangulation. Clinical presentation of stomal intussusception is clinically identical.

7.7.1.4 Diagnosis

It is important to stress that in a patient with a stoma, it should be evaluated for possible local obstruction. Stomal intussusception is easily confused with stomal prolapse [257], which is easily reducible and rarely accompanied with stomal obstruction. If the stoma is the cause of obstruction and MRI is not available, ionizing diagnostic modalities could be excluded from the diagnostic algorithm.

7.7.1.5 Treatment

Intussusception

In all cases during pregnancy, stomal intussusception was treated surgically. Surgical management was different in all three cases: (1) by revision of ileostomy [255], (2) by resection and refashioning of the colostomy [257], and (3) reduction by gentle traction at laparotomy, the lateral space to the stoma was closed, and the ileum attached to the anterior abdominal wall with absorbable sutures [256].

Prolapse

In general population, stomal prolapse is treated conservatively if asymptomatic and without complications such as obstruction, necrosis, or strangulation. Prolapse can be reduced manually or sugar applied on the prolapsed segment [258]. Even incarcerated prolapse can be successfully treated with these measures [259]. These simple methods avoid operation and anesthesia and can sometimes postpone definitive treatment after delivery. If irreducible prolapse becomes ulcerated or strangulated or causes intestinal obstruction, immediate surgical treatment is mandatory.

Increased abdominal pressure may occasionally cause an ileostomy prolapse. This usually occurs in patients who have had an ileostomy placed less than a year before becoming pregnant. This data should be taken with caution because temporary ileostomies are almost always closed within 3–6 months.

7.7.1.6 Prognosis

Maternal survival after operative treatment of intussusception is 100% [10, 255–257]. In the only case [256], both twins survived and were normal after CS in 35th week when fetal distress occurred.

7.7.2 Extraluminal Stomal Compression

7.7.2.1 Incidence

This is extremely rare with several cases published [260, 261].

7.7.2.2 Diagnosis

Plain abdominal X-rays lack sensitivity and specificity in the gravid patient. In addition, it is more difficult to locate the level of intestinal obstruction in the pregnant patient. Abdominal MRI can delineate the site of obstruction, sometimes with the addition of endoscopy (Fig. 7.40). Since 2007, two

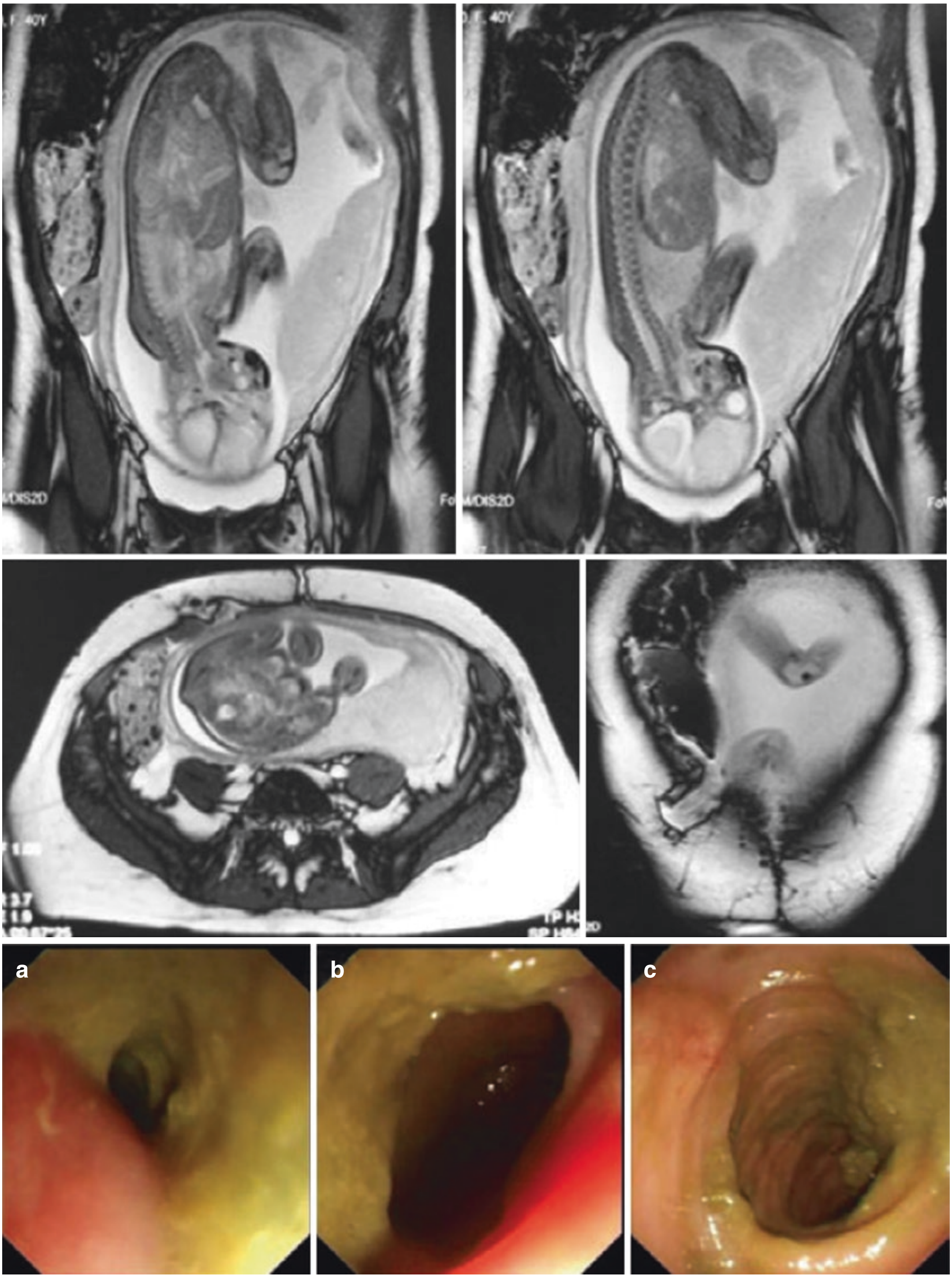

Fig. 7.40 Abdominal MRI revealing fecalization and distention of the distal ileum terminating just proximal to the end ileostomy at a site compressed by the adjacent gravid uterus and fetus. Below the MRI is a sequence of photographs showing the endoscopic view through the stoma of the distal ileum, demonstrating (**a**) and (**b**) evident extrinsic compression with a thickened, inspissated ileal content and (**c**) normal distal ileal appearances present more proximally. Reproduced with permission from [260]

cases have been published in which MRI was used to correctly diagnose and differentiate ileostomy obstruction caused by compression by gravid uterus [260, 261]. In both cases, surgical intervention was avoided, and there was a return to normal stomal function immediately postpartum. It should be noted that adhesions (assumed to be the major cause of bowel obstruction in pregnancy) are not visible on MRI cross-sectional images; their presence is inferred from the absence of obstructing lesions such as a gravid uterus [261].

7.7.2.3 Treatment and Prognosis

Gestational intestinal obstruction has previously been associated with very significant maternal and fetal mortality and morbidity, and so the prevailing consensus in the (limited) literature strongly favored aggressive management by urgent surgical intervention in all cases of stomal obstruction [10, 21, 262].

In contrast, recent case reports suggest that ileostomy obstruction caused by the enlarging gravid uterus rather than adhesions may be more common than previously recognized (see Sect. 7.7.2.2) [263]. It is extremely important to distinguish between ileostomy obstruction caused by adhesions and those caused by mechanical compression on the stoma itself since treatment for the latter is conservative rather than surgical [261]. Stenting and drainage of the blocked ileostomy by tube or variant have been used in several cases with no complications [260, 264]. A wide-bore drainage tube can be used to bridge the compressed portion of bowel [265] or an endotracheal tube to unblock the distorted nipple valve of a Kock's pouch that became obstructed by the enlarging uterus [264]. Other nonsurgical techniques reported to be successful include ileal lavage, massage, hot water bottles, and an elemental diet [254, 255, 265].

7.8 Sigmoid Volvulus

7.8.1 Incidence

Sigmoid volvulus is the most common cause of large bowel obstruction complicating pregnancy, accounting for 3.1–12.5% [266, 267], in some series up to 25–44% [55]. In endemic regions for Chagas disease, in South America, digestive manifestations are common, and sigmoid volvulus is a possible complication during pregnancy [268]. Sigmoid volvulus in pregnancy accounted for 2% of all sigmoid volvulus in the Mayo Clinic between 1960 and 1980 [267].

Sigmoid volvulus was first described in general population by von Rokitansky in 1837 [269]. The initial report in pregnancy at term was by Braun in 1885 [270]. The patient died, and the diagnosis was made at autopsy. Six years later, the first case reported in the United States was described by Cattell. More than 100 cases of sigmoid volvulus have been reported in the pregnancy and puerperium (Table 7.10). Lambert [271] reported 29 cases of sigmoid volvulus before 1931, followed by another 12 cases by Kohn et al. [272] between 1931 and 1944.

7.8.2 Pathophysiology and Risk Factors

Pregnancy itself is considered to be the precipitating factor for sigmoid volvulus. Even Braun in 1885 believed that the pressure of the gravid uterus upon the sigmoid flexure produced obstinate constipation which preceded the attack and gave rise to elongation of the mesentery and bowel above the seat of compression, to a sufficient extent to cause volvulus [270], the hypothesis confirmed by others [46, 290]. The colon rises out of the pelvis and twists around the fixation point on the sigmoid colon and its mesocolon. This mechanism may lead to mechanical obstruction and vascular compromise of the bowel [267]. This could probably explain the increased incidence of sigmoid volvulus in the third trimester [6, 286]. Almost all cases of the sigmoid volvulus develop during the third trimester (Table 7.10). Despite this higher propensity in the third trimester, there have been reports of this complication developing in the early pregnancy as well as the puerperium (Table 7.10). Sigmoid volvulus in pregnancy affects mainly chronically constipated patients

Table 7.10 Reported cases of sigmoid volvulus in pregnancy

Authors	Year	Cases	Gestational age (weeks)	Duration of symptoms (h)	Outcome	
					Mother	Fetus
Lambert AC [271]	Before 1931	29	–	–	–	–
Kohn SG [272]	1931–1944	12	–	–	–	–
Harer WB Jr [46]	1944–1958	11	–	–	–	–
Lazaro EJ [273]	1958–1969	13	–	–	–	–
Fraser JL	1983	1	32	24	Healthy	Alive
Ballantyne GH [267]	1985	1	Third trimester	–	–	–
Hofmeyr GJ [274]	1985	2	33	72	Healthy	IUD
			26	72	Expired	IUD
Keating JP [275]	1985	1	34	24	Healthy	Alive
Allen JC	1990	1	28	24	Healthy	Alive
Lord SA	1996	1	36	24	Healthy	Alive
Joshi MA	1999	1	28	24	Healthy	IUD
De U [276]	2005	1	24	72	Healthy	IUD
Alshawi JS [184]	2005	1	28, 35	24	Healthy	Alive
Iwamoto I [277]	2007	1	35	72	Expired	IUD
Vo TM [278]	2008	1	28	24	Healthy	Alive
Narjis Y	2008	1	24	–	Healthy	Alive
Atamanalp SS	2008	9	Third trimester	24	Healthy	–
			Second trimester	36	Healthy	–
			Third trimester	72	Expired	–
			Third trimester	20	Healthy	–
			Third trimester	24	Healthy	–
			Second trimester	36	Healthy	–
			Third trimester	12	Healthy	–
			First trimester	22	Healthy	–
			Third trimester	18	Healthy	–
Chourak M [279]	2009	1	37	48	Healthy	IUD
Kolusari A [280]	2009	3	7	24	Healthy	Alive
			31	48	Healthy	IUD
			32	48	Healthy	Alive
Machado NO [281]	2009	1	18	18	Expired	Alive
Togo A [282]	2011	1	25	48	Healthy	Alice
Khan MR [283]	2012	1	30	144	Expired	IUD
Dray X [284]	2012	1	37	12	Expired	Alive
Nascimento EFR [285]	2012	1	33	72	Expired	IUD
Aftab Z [286]	2014	1	32	48	Healthy	Alive
Palmucci S [287]	2014	1	31	72 + 48	Healthy	Alive
Kessler LC [288]	2014	2	30	24	Healthy	Died
			38	120	Healthy	Alive
Atamanalp SS [289]	2015	1	16	48	Healthy	–
Al Maksoud [290]	2015	1	26	120	Healthy	Alive
Serafeimidis C [291]	2016	1	30	48	Healthy	Alive
Ward KE [292]	2017	1	Labor/puerperium	24?	Healthy	Alive

IUD intrauterine death

with a long redundant sigmoid colon as in general population [267]. High-fiber diets are also a predisposing factor [266] probably due to voluminous, heavy fecal mass that is prone to position changes due to inertia.

7.8.3 Clinical Presentation

The diagnosis of sigmoid volvulus should be suspected when a pregnant female presents with a clinical triad of abdominal pain, distention, and

constipation. The pain can be intense from the beginning or gradually increasing in intensity, colicky in nature. Initially, it is not associated with vomiting, fever, or anal bleeding [286]. New onset vomiting progresses to fecal vomiting. In the course of the disease, the patient may present with fever, dehydration, and absence of bowel sound. The average time from the onset of obstructive symptoms until the presentation is 24–48 h but as long as 6 days has been reported (Table 7.10). Largely, this is because pregnancy itself masks the clinical picture since abdominal pain, nausea, and leukocytosis can occur in an otherwise normal course of pregnancy [275].

7.8.4 Diagnosis

7.8.4.1 Laboratory Findings

The leukocytosis can be a consistent sign but in the first phase of the disease can be normal or slightly elevated [184]. Furthermore, the white cell count is normally elevated in pregnancy. In the early phase, most laboratory findings are normal. When metabolic derangements due to bowel necrosis and sepsis develop, abnormal laboratory findings are a rule.

7.8.4.2 Plain Abdominal X-Ray

Plain abdominal X-ray is necessary for the diagnosis of intestinal obstruction or volvulus (Fig. 7.41) and fortunately almost always sufficient for definitive diagnosis. *Coffee bean sign* can be found or can be slightly distorted due to enlarged uterus. *Frimann-Dahl's sign*: three linear shadows converging to the left side—a radiographic sign of sigmoid volvulus is difficult to find in pregnancy due to the distorted anatomy of that region.

7.8.4.3 Abdominal MRI

Abdominal MRI has high sensitivity and specificity for diagnosing sigmoid volvulus. Pathognomonic imaging findings, showing the *coffee bean sign*, the *U-shaped distended sigmoid loops*, the *northern exposure sign*, and the twisting of the sigmoid loop (Fig. 7.42), can be clearly seen.

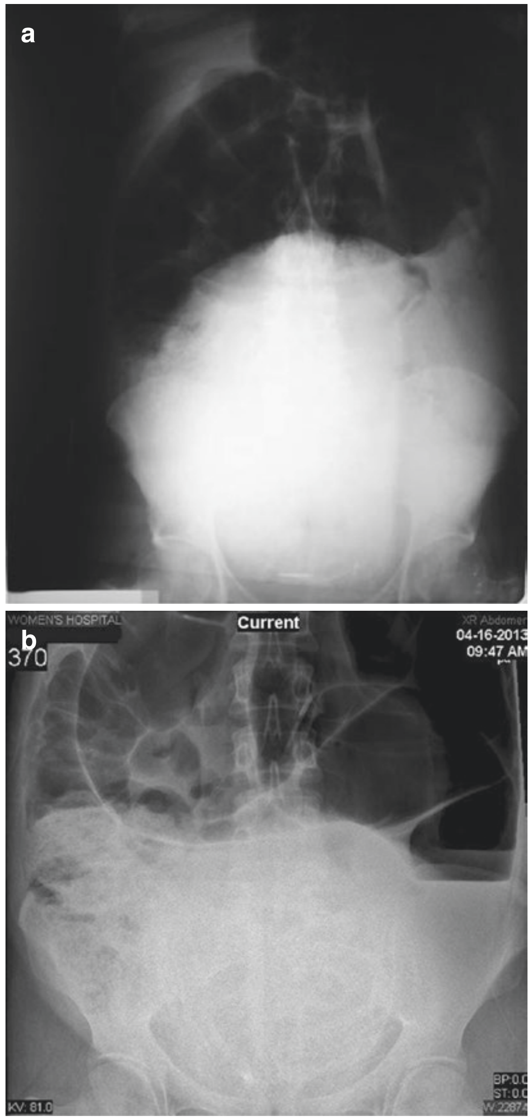

Fig. 7.41 Plain abdominal radiographs showing sigmoid volvulus in pregnancy. The characteristics of the sigmoid volvulus (*coffee bean sign*) are distorted due to the enlarged uterus (**a**) at 25 weeks [282] and (**b**) at 31 weeks gestation. Reproduced from [286] under the CC BY 2.0

7.8.5 Treatment

7.8.5.1 Endoluminal Decompression

In the first trimester, a nonoperative procedure using colonoscopic detorsion and rectal tube decompression is recommended until the second trimester when sigmoid colectomy is performed for recurrent cases [184]. In addition, mucosal

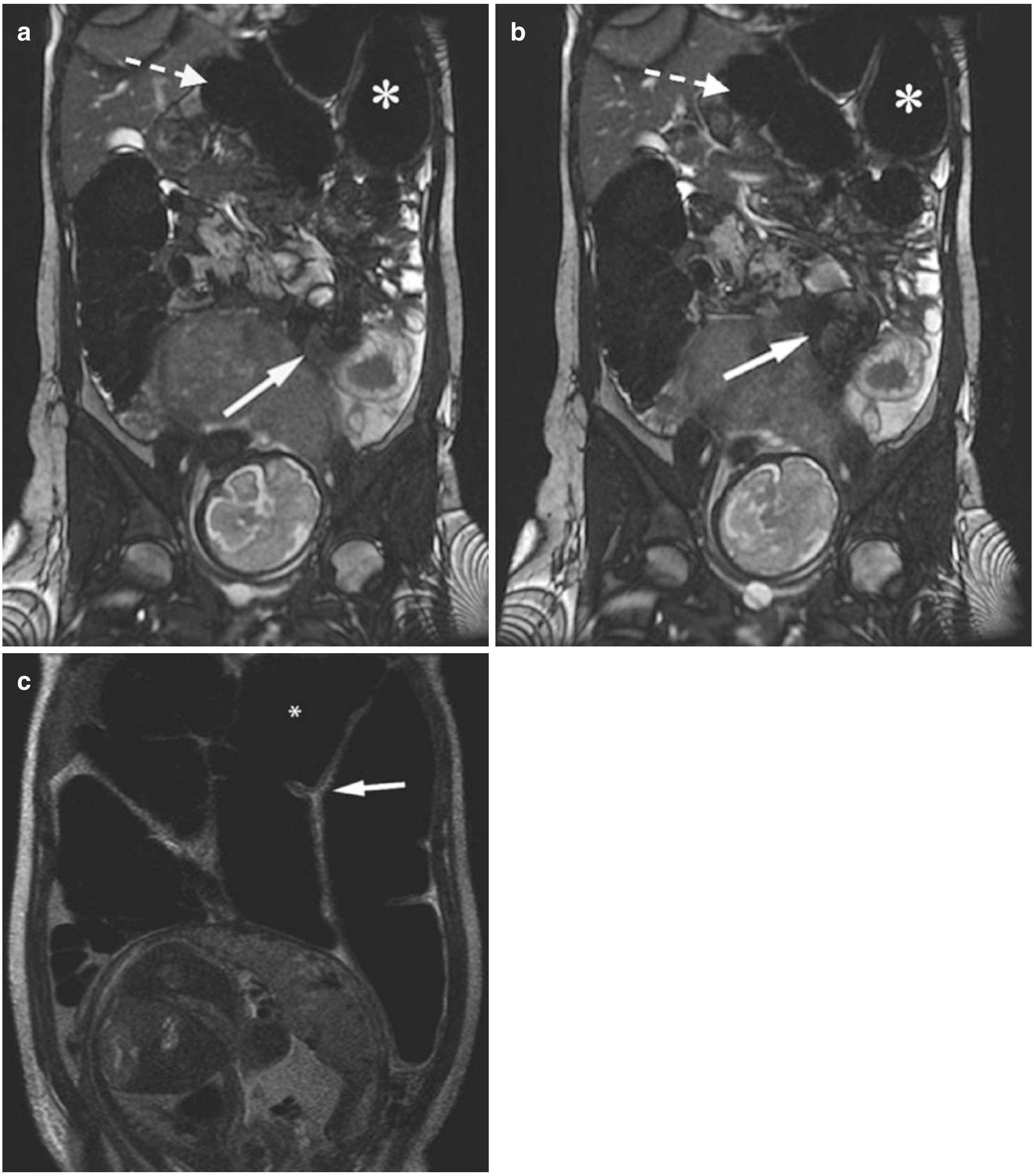

Fig. 7.42 Abdominal MRI at 31 weeks gestation. (**a**, **b**) The distended sigmoid loop—with an inverted "U configuration" (*white asterisks*)—extended cephalad to the transverse colon (*white-dotted arrows*) up to the left hemidiaphragm. The displacement of the sigmoid colon cephalad to the transverse colon produces the *northern exposure sign*. The figures also show the partial twisting of the sigmoid loop (*white arrows*) resulting in dilation and obstruction. (**c**) *Coffee bean sign* recognizable between two closed and dilated apposed loops, recalling the appearance of a "coffee bean." The central cleft of the coffee bean is due to the opposing bowel wall (*white arrow*). The *U-shaped distended sigmoid loop* is also well depicted: a distended ahaustral sigmoid loop (*white asterisk*), with an inverted "U configuration," extended up to the left hemidiaphragm; the transverse colon is dilated and displaced to the right side by the U-loop. Reproduced with permission from [287]

ischemic changes can be detected by colonoscopy. If mucosa is vital, endoscopic decompression can be tried. If signs of mucosal ischemia are found, emergent laparotomy with sigmoid resection is mandatory. In the third trimester, the same principles should be applied until fetal maturity and delivery when sigmoid colectomy is performed [184].

7.8.5.2 Surgical Treatment

The management of volvulus with or without perforation in pregnant women is similar to that of nonpregnant women. The aim of surgical treatment is to remove the obstruction without a risk of recurrence. The basis of therapy is early surgical intervention. In the absence of peritonitis and during the second trimester of gestation, some recommend detorsion by mini-laparotomy [276]. Such algorithm was found in 1950 to shorten the operation, while the sigmoid resection with anastomosis was performed after puerperium [293]. Sigmoid resection is recommended due to the high incidence of recurrence [183, 184]. Some authors recommend the anastomosis after sigmoidectomy during the first and second trimesters [294]. It is safer to perform Hartmann's procedure eliminating the risk of anastomotic dehiscence with deleterious consequences on the mother and fetus. It should be remembered that growing uterus could compress the anastomosis causing ischemia or compress colon distal to anastomosis increasing the risk of anastomotic dehiscence. In the third trimester, if sufficient intestinal exposure cannot be obtained due to the enlarged uterus, a CS must be carried out [295]. After detorsion, the deflated loop could be on the left side of the abdomen and should be replaced without even treating the uterus. This could be done by slipping the loop of bowel over the fundus of the uterus (Fig. 7.43). Probably, compression of the uterus could be contributing factor in obstruction when volvulus is partial (Fig. 7.44). The entire bowel should be examined for other areas of obstruction. Intestinal viability should be assessed cautiously. If viable it can be just

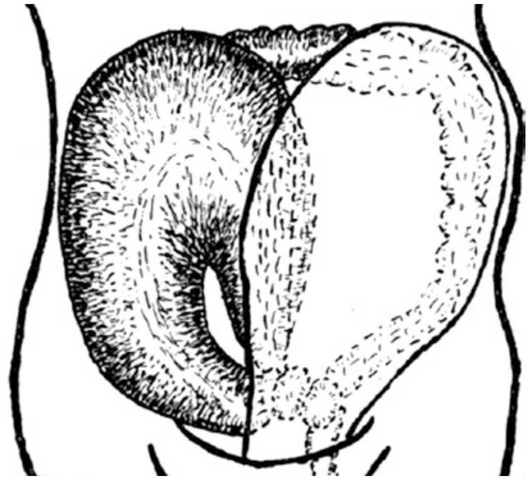

Fig. 7.43 Diagram showing relative positions of the uterus on the right and sigmoid volvulus on the left and behind the uterus. Reproduced with permission from [293]

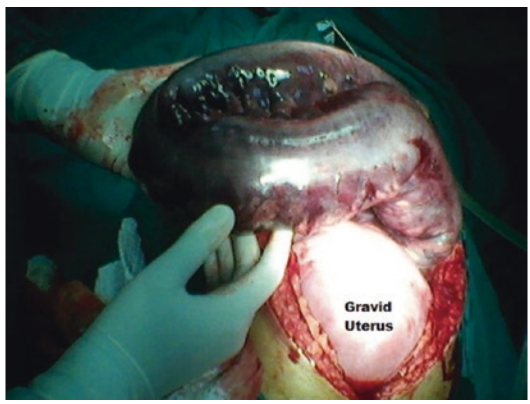

Fig. 7.44 Dilated ischemic sigmoid colon which had undergone volvulus compressed by gravid uterus. Reproduced with permission from [290]

derotated and left in situ [287, 291], but recurrent sigmoid volvulus in general population is around 50%; therefore, resection, during the same operation with or without anastomosis, is recommended [295]. The more secure option is to perform the colostomy after sigmoid colon resection because anastomotic dehiscence leads to stercoral peritonitis which can cause abortion and preterm labor in addition to maternal complications.

7.8.6 Prognosis

A delay in diagnosis and surgical intervention had a significant impact on the ultimate outcome of the mother and fetus [46]. The delay in diagnosis of sigmoid volvulus may lead to bowel infarction and necrosis [291] with hypovolemia, electrolyte disturbances, renal failure, metabolic acidosis, septic shock, and multiple organ failure. The maternal and fetal outcome has been directly related to the degree of bowel ischemia and subsequent sepsis. Maternal and fetal mortality for the period 1978–2012 was 20% and 40%, respectively [283]. Maternal mortality has been reported to be 5% if the bowel is viable but rises to over 50% if perforation has occurred.

The majority of maternal and fetal deaths occurred when a delay in presentation and surgical intervention was more than 48 h.

This observation highlights the fact that early intervention is vital in cases of sigmoid volvulus for both the mother and the fetus.

7.9 Cecal Volvulus

During pregnancy and the puerperium there should not be much delay in performing laparotomy in doubtful cases.

J. H. Spence, 1937

In view of the rapid change of position of the intestines after delivery of a full-term child, it is perhaps surprising that volvulus does not happen more frequently.

J. H. Spence, 1937

7.9.1 General Considerations

Volvulus of the cecum is torsion of the bowel around its own mesentery that results in a closed-loop obstruction. Cecal volvulus can occur in 11–25% of the population who has hypermobility of the proximal colon because of inadequate lateral peritoneal fixation during development [10, 160]. Furthermore, the distal ascending colon must be fixed, resulting in a pivot point around which the cecal rotation may occur. While this point of fixation is typically the normal congenital peritoneal attachments, other possibilities include postoperative adhesions or an abdominal mass. In pregnancy, the enlarged uterus may displace any redundant or abnormally mobile cecum out of the pelvis. Partial obstruction may occur from uterine pressure or from kinking of the colon at a fixed point. The ensuing distention raises the colon even higher, producing torsion at this fixed point [46, 296].

7.9.2 Historical Perspective

The first published case in pregnancy was by White in 1914. The 26-year-old in her 33-week second pregnancy was constipated for 6 years after the drainage of the abscess of appendicular origin with an incisional hernia (presumably midline incision). The patient then expelled the stillbirth, and after several days indication for the operation was made. The cecal and ascending colon gangrene due to volvulus was found. Resection was performed, but the patient died [297]. Basden in 1934 reported the case of a woman in labor in whom laparotomy with CS was done for a suspected intra-abdominal condition and a volvulus of the cecum was found [298]. Spence in 1937 quoted a case of volvulus shortly after delivery in which too much attention was paid to the associated uterine infection. He stated that *during pregnancy and the puerperium there should not be much delay in performing laparotomy in doubtful cases* [299]. This recommendation of that time was confirmed in 1941 when a patient presented 17 h after delivering stillborn by forceps. During extensive diagnostic workup, the patient died, and at necropsy volvulus of the cecum and part of ascending colon was found [300].

7.9.3 Incidence and Risk Factors

Cecal volvulus occurs approximately 1/500,000 pregnancies but may be as low as 1/1,000,000 [301]. Cecal volvulus in pregnancy accounted for

2% of all colonic volvulus in the Mayo Clinic between 1960 and 1980 [267]. In 1944, out of 79 reported cases of volvulus in pregnancy, 19 were of the right colon [272].

In 1944, multiparity, due to the abdominal wall laxity, was defined as a risk factor. Fixed cecum due to adhesion from the previous operations is a predisposing factor for volvulus [302]. Age did not appear to affect the incidence [272].

7.9.4 Clinical Presentation

Classically, cecal volvulus presents as bowel obstruction, similar to sigmoid volvulus (see Sect. 7.8.3). The symptoms and findings at clinical examination are often vague and indistinguishable from the usual symptoms attributed to late pregnancy or other causes of an acute abdomen. Vomiting is more common with cecal than sigmoid volvulus. With sigmoid volvulus, the ileocecal valve can be competent (for some period during distal obstruction). The condition was diagnosed before laparotomy in only 25% of the cases [46, 296].

7.9.5 Differential Diagnosis

In pregnancy, cecal volvulus may be mistaken for placental abruption, degenerating fibroids, a ruptured uterus, hyperemesis, and torsion of the ovary, extrauterine pregnancy, acute polyhydramnios, cholecystitis, appendicitis, urinary tract infections with or without urolithiasis, and other causes of bowel obstruction [303, 304].

7.9.6 Diagnosis

Plain abdominal X-ray has a high sensitivity for the diagnosis of cecal volvulus in pregnancy [305], but sometimes obstruction can only be recognized on plain abdominal radiographs (Figs. 7.45 and 7.46). The diagnosis may be obscured if the closed loop is filled with fluid, oriented in an anteroposterior plane, or overlain

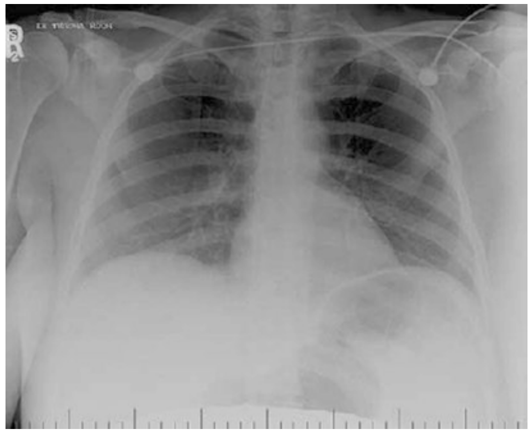

Fig. 7.45 Erect chest radiograph showing dilated air-filled bowel loops under the left hemidiaphragm. Shielding of the lower abdomen is present. Reproduced with permission from [302]

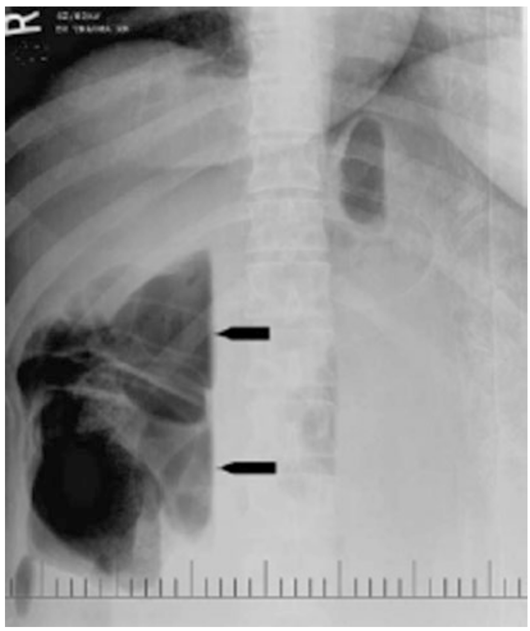

Fig. 7.46 Right lateral decubitus radiograph showing dilated loops of bowel with air-fluid levels (*arrows*). Reproduced with permission from [302]

by loops of air-distended bowel. The intermittent abdominal pain may be misinterpreted as uterine contractions, and emergency CS for intestinal volvulus has been described [296].

When CT is considered appropriate, a senior radiologist should always be involved in the decision-making process to avoid overutilization of a potentially harmful test. Low-dose CT

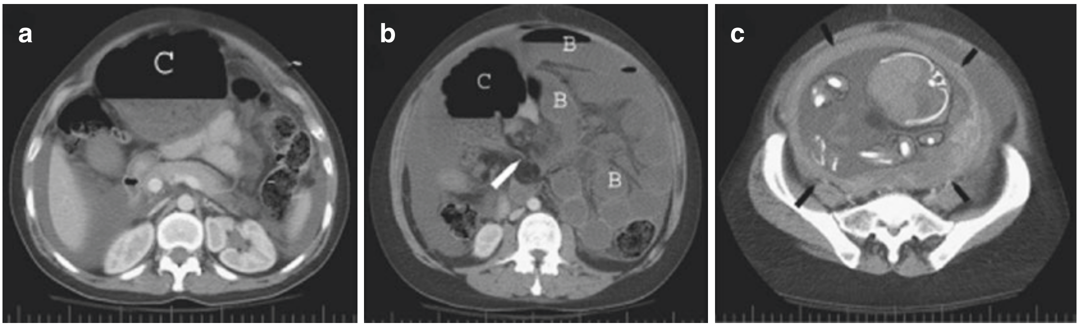

Fig. 7.47 (**a**) Axial abdominal CT showing a dilated cecum with an air/feces level in the mid-upper abdomen. (**b**) The dilated cecum (*C*) shows progressive tapering terminating at the site of torsion (*white arrow*) resulting in the appearance of a *bird's beak*. Dilated fluid-filled loops of small bowel are shown (*B*). The lack of normal mural enhancement of the cecum on CT, compared with the normally enhancing small bowel loops, is suggestive of ischemia. The cecum was subsequently found to be necrotic at surgery. (**c**) Axial views of the lower abdomen show the gravid uterus (*black arrows*). Reproduced with permission from [302]

Fig. 7.48 Abdominal CT in 21 weeks gestation showing cecal volvulus. The cecum is distended in the right upper quadrant. There is no colonic distention distally from the cecum. There are multiple loops of distended small bowel. Reproduced with permission from [307]

protocols for imaging the acute abdomen in pregnancy minimize fetal irradiation. CT has high sensitivity and specificity for delineating cecal volvulus in pregnancy (Figs. 7.47 and 7.48).

MRI is increasingly used in pregnant patients. MRI has been used extensively in the characterization and staging of neoplastic disease in pregnant women and is increasingly used in the evaluation of the acute abdomen. Abdominal MRI is accurate for the diagnosis of acute appendicitis in pregnancy (see Chap. 1). Abdominal MRI may potentially be of benefit in demonstrating the site of transition in bowel obstruction and identifying areas of inflammation, abscess formation, or hemorrhage within the abdomen and pelvis [306].

7.9.7 Treatment

In the first half of the twentieth century, surgical options were cecopexy and cecostomy [308]. Current surgical options include cecal detorsion open or laparoscopic [309] with or without appendectomy, colonic detorsion, and either cecopexy or cecostomy and right hemicolectomy if the necrotic bowel is found. Evidence from general and pregnant population suggests that recurrence (even in the same pregnancy) of cecal volvulus due to the hypermobile cecum, with either detorsion, cecopexy, or cecostomy, is unacceptably high [304, 310].

> Right hemicolectomy is the treatment of choice for cecal volvulus in pregnancy.

7.9.8 Prognosis

7.9.8.1 Maternal and Fetal Outcome

Up to 1940, due to the complex clinical picture and limited diagnostic modalities, both maternal and fetal mortality was 26.3%, while during last several decades, there was no maternal mortality [311].

7.10 Incarcerated Internal Hernia

7.10.1 Post-Bariatric Surgery

7.10.1.1 Introduction

There has been a dramatic increase in the number of bariatric surgeries performed for the management of morbid obesity, with Roux-en-Y gastric bypass (RYGB) comprising the most frequent procedure performed in the United States [312, 313]. Women comprise 80% of the patients and 75% are 18–49 years of age [314]. Recently, sleeve gastrectomy is gaining popularity due to the similar results and technically easier operation. Weight loss is likely to reduce infertility and increase sexual activity, leading to increasing pregnancy rates in such females. The health risks experienced by obese women during pregnancy can be reduced by the weight loss induced by bariatric surgery [315], but these patients are at risk of bariatric surgical complications during their pregnancies.

7.10.1.2 Classification

Women who have undergone RYGB are at risk of: (1) internal hernias, (2) intussusception (see Sect. 7.2), and (3) adhesive small bowel obstruction during pregnancy (see Sect. 7.4), which can lead to maternal and/or fetal death [316].

The internal hernia has been estimated to occur in up to 5% of patients following laparoscopic RYGB for morbid obesity in general population [317]. This rate is higher than when this surgery is performed using an open approach, attributed to greater adhesion formation that tethers and immobilizes small bowel loops, preventing their passage through surgically created mesenteric defects [318–320]. Modifications of the initial bypass procedure to lower the risk of subsequent internal hernia are not fully effective. For instance, although it has become common to suture all mesenteric defects at the time of initial surgery, the rapid weight loss that occurs postoperatively predisposes to a widening of suture lines and reopening of these defects [312, 313, 320].

The most common site of herniation following laparoscopic RYGB is through a surgical defect in the transverse mesocolon, which is created when using a retrocolic approach in forming the anastomosis between the Roux limb and gastric pouch. Although some surgeons may opt to use an antecolic approach to avoid the creation of such a defect, it remains possible for small bowel to herniate through a surgical defect in the small bowel mesentery or through a defect between the Roux limb mesentery and the transverse mesocolon, constituting a so-called *Petersen's hernia* (Fig. 7.49).

Although an internal hernia in this setting is challenging to diagnose clinically given the nonspecific and often subtle presentation, a delay in diagnosis and operative treatment may result in dire consequences, including bowel incarceration, ischemia, gangrene, sepsis, and possibly death [312, 318, 321]. Indeed, over 80% of gastric bypass surgeries in the United States are performed in female patients [322], frequently of childbearing age [313, 318]. The significant weight loss that results from the surgery has been found to improve fertility and increase sexual activity, such that pregnancy commonly occurs in patients with a history of RYGB [313, 316, 318, 320].

7.10.1.3 Incidence

The incidence of an internal hernia after laparoscopic RYGBP in general population is 3.1% [324]. In 2004, Moore et al. provided the first report of a transmesenteric internal hernia following RYGB occurring in a pregnant patient [316]. Up to 2016, 27 pregnant patients with internal hernia following RYGB were described [312, 313, 316, 318, 320–322, 325–331]. It is suggested that pregnancy may contribute to the development of an internal hernia secondary to increased abdominal pressure and superior displacement of small bowel loops by the enlarged gravid uterus with most cases in advanced

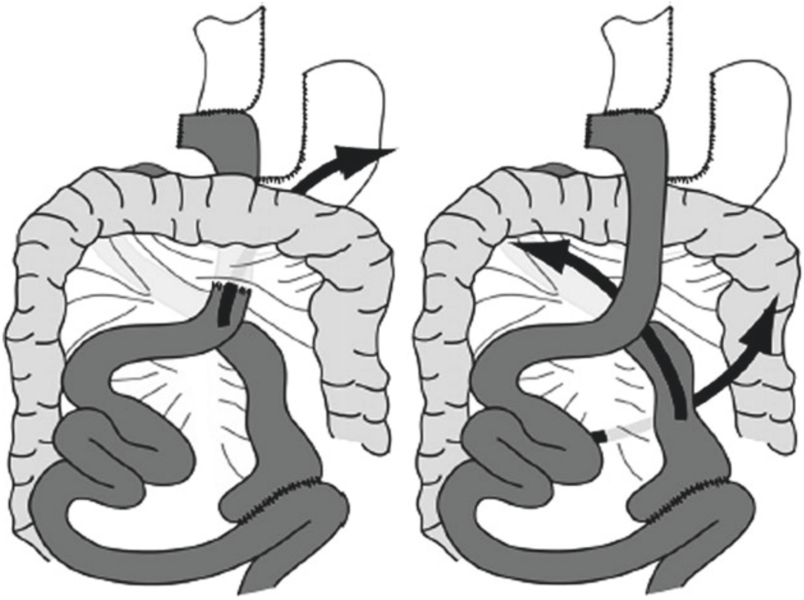

Fig. 7.49 Diagram of the internal hernias that may occur following laparoscopic RYGB. A hernia through the transverse mesocolon defect is the most common following laparoscopic RYGB but only with a retrocolic approach. With an antecolic approach, it is possible for the small bowel to herniate through the space between the Roux limb mesentery and the transverse mesocolon (*Petersen's hernia*) or through the surgically created small bowel mesenteric defect. These later two hernias may uncommonly occur in the setting of a retrocolic approach. Reproduced with permission from [323]

pregnancy [312, 313, 318, 320, 329]. There is a wide interval between RYGB and the time of an internal hernia, ranging from 6 months to 9 years [312, 313, 316, 318]. The possibility of developing an internal hernia following gastric bypass surgery is a lifelong risk [313]. It is notable that almost 50% of the cases [312, 318, 329–331] occurred within a year of RYGB, in view of the recommendation that women avoid pregnancy for at least 1 year following the procedure to allow for complete wound healing and stabilization of weight [312, 313, 318]. Petersen's hernia occurred mostly in the third trimester than in the second and infrequently in the first trimester [320, 321, 328].

7.10.1.4 Clinical Presentation

One of the most important aspects of the long-term postoperative care of gastric bypass patients is the prompt diagnosis and treatment of the patient who presents with abdominal pain and obstructive symptoms. In patients who have undergone gastric bypass for morbid obesity, internal hernias of the small bowel, with or without bowel obstruction, can develop and can be catastrophic. Patients can present with severe epigastric pain or periumbilical pain, initially cramping, and seek to find a position of comfort, either leaning forward or on their side. Patients typically have nausea and retching. The laboratory evaluation is often relatively normal at presentation; this can delay appropriate care if physicians are not experienced in the care of these patients. Plain abdominal X-rays often do not show typical signs of obstruction such as air-fluid levels or dilated loops of bowel, and the findings can be misleading.

Once internal hernias occur, the obstructed afferent limb of duodenum presents no typical symptomatology suggestive of intestine obstruction [331]; therefore, progression from obstruction to strangulation and ischemia develops. Laboratory findings provide no help in differentiation. Instead, the impression could initially be

the diagnosis of conditions such as gastritis, peptic ulcer perforation, or acute pancreatitis.

7.10.1.5 Diagnosis

Abdominal CT

There has been increasing awareness by the radiology community of the risk of an internal hernia following gastric bypass surgery, as well as of the critical nature of establishing the diagnosis, with numerous recent studies in the radiology literature demonstrating the ability of abdominal CT to diagnose an internal hernia following RYGB [319, 332]. In 6/12 reports [313, 318, 320, 322, 329], the CT appearance of an internal hernia is demonstrated. In an additional three reports, the CT findings assisted in the diagnosis [312, 331]. The CT findings noted in these cases match the characteristic CT findings of an internal hernia following RYGB described in the radiology literature, including an abnormal cluster of small bowel loops and displacement, engorgement, and stretching of the mesenteric vessels [332]. Four of the articles maintain that CT should be obtained promptly, even in the pregnant patient, given increased recognition of the appearance of an internal hernia using this method [313, 316, 320, 322].

Abdominal CT scan with oral and intravenous contrast is the best radiological tool for evaluation in gastric bypass patients who present with obstructive symptoms of internal hernias. The interpretation of the CT scan by an experienced bariatric surgeon and radiologist experienced in bariatric patients can often make the diagnosis of the altered anatomy of an internal hernia [319]. The risk of radiological imaging of the pregnant patient using CT is a major concern, but the benefit is these scenarios overweight the radiation risks.

Abdominal MRI

The various findings identified on MRI match the previously reported CT findings of an internal hernia [332]. It is noted that the mesenteric vessels were not optimally assessed as intravenous gadolinium chelate was not administered; however, such an assessment was not ultimately required for making the diagnosis in this particular case. Previous reports have shown the utility of MRI in the pregnant patient for diagnosing other small bowel abnormalities, including obstruction from postoperative adhesions and ventral hernia. It seems reasonable that MRI could have utility in establishing the diagnosis of an internal hernia; however, MRI cannot replace CT for this diagnosis in all cases. For instance, the only suggestive findings in some cases may involve changes in the mesenteric vasculature, which would not be optimally assessed by unenhanced MRI (Fig. 7.50). Furthermore, MRI may not be available on an emergent basis in all institutions. CT remains an option in cases in which MRI cannot be performed or in which the diagnosis remains equivocal following MRI.

Based upon this report, MRI should at least be considered during the evaluation of a pregnant patient with a history of RYGB who presents with abdominal pain, as this approach may enable a confident diagnosis without the use of ionizing radiation [323].

7.10.1.6 Treatment

The policy for gastric bypass patients presenting with intestinal obstructive symptoms with the possibility of an internal hernia typically includes rapid evaluation by abdominal CT scan. If CT could not be performed, there should be a low threshold to proceed to diagnostic laparoscopy/laparotomy on the basis of clinical symptoms alone.

Treatment depends on the vitality of the bowel. If gangrenous changes are present, then segmental resection with anastomosis is indicated (Fig. 7.51). If a long limb is gangrenous, resection should be followed by new gastroenterostomy and jejunojejunostomy. Since the three cases (27%) were diagnosed in the third trimester and had exploratory surgeries performed within 2 days of admission, the conclusion drawn is that the cases of the third trimester had serious bowel strangulation due to high pressure. Moreover, due to high fetal survival rate in the third trimester, the decision to perform an exploratory laparotomy is made more easily without hesitation than in other trimesters.

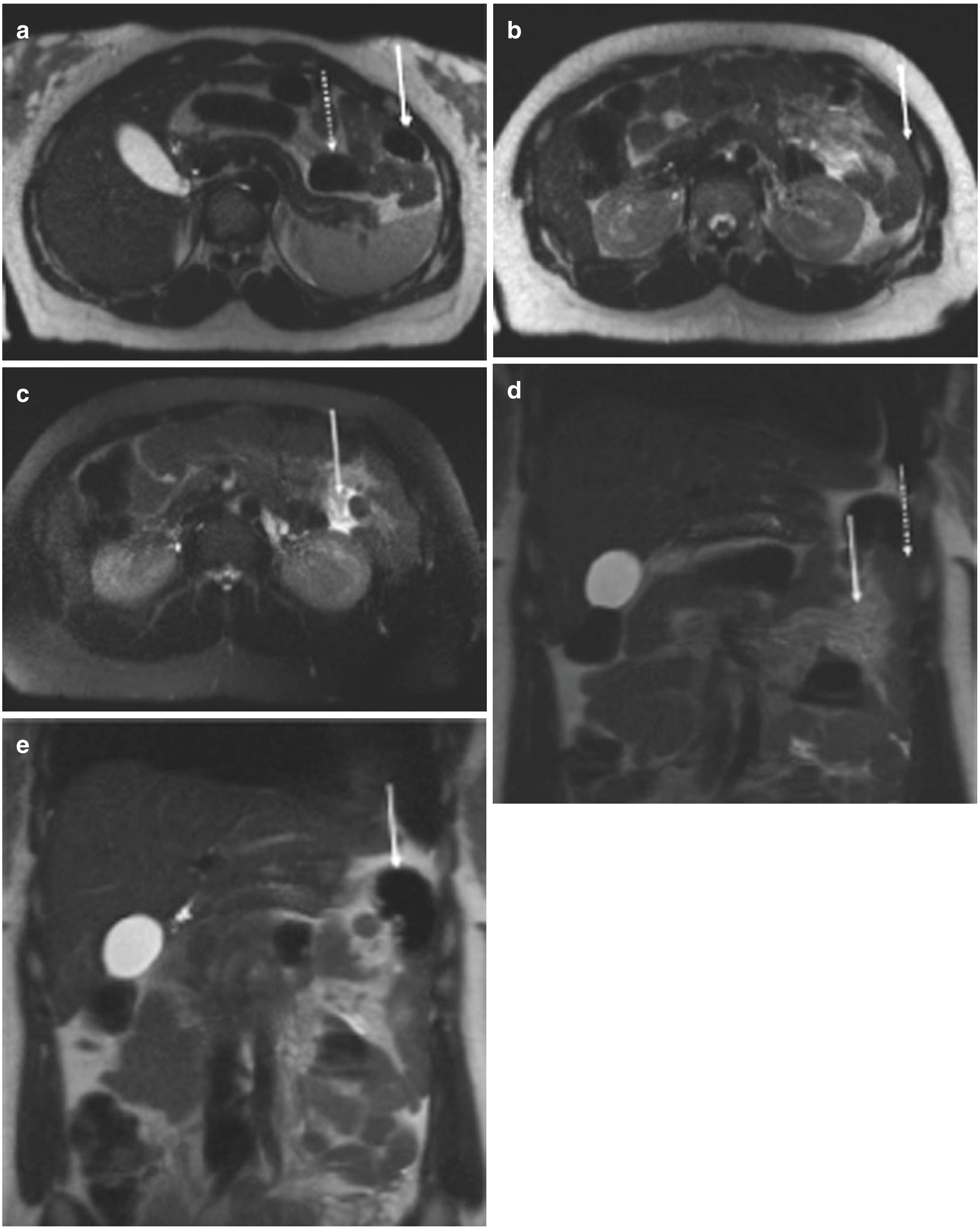

Fig. 7.50 Axial MRI (**a**) and (**b**) demonstrate a cluster of small bowel loops in the left upper quadrant, including a dilated loop (*solid arrow*, **a**), that overlie a centrally displaced segment of the transverse colon (*dotted arrow*) and show no overlying omental fat (*solid arrow*, **b**). Axial MRI (**c**) demonstrates mesenteric edema in this region (*solid arrow*). Coronal MRI (**d**) demonstrates herniation of fat with prominent vessels through a mesenteric defect (*solid arrow*) as well as the abnormally positioned loops of the small bowel within the far *left lateral* aspect of the abdominal cavity with an absence of overlying omental fat (*dotted arrow*). An additional coronal MRI (**e**) confirms the presence of the dilated loop of the small bowel in the left upper quadrant (*solid arrow*). Reproduced with permission from [323]

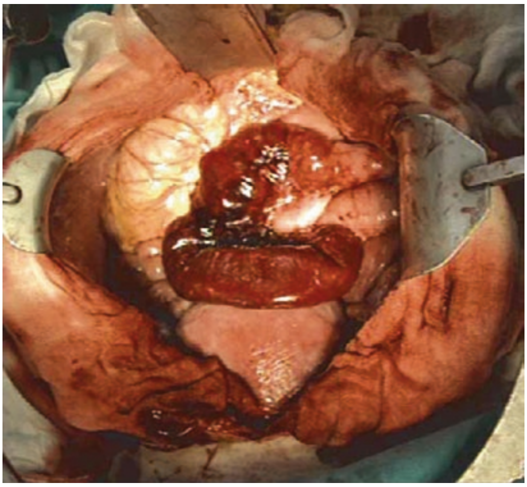

Fig. 7.51 After Cesarean delivery, an exploratory laparotomy demonstrated a gangrenous change of the upper jejunum due to fibrous band involving the afferent limb near the site of the Roux-en-Y anastomosis. Segmental resection (20 cm) of the nonviable bowel was performed. Reproduced with permission from [330]

7.10.1.7 Prognosis

Maternal Outcome

The mother survived in all [11] cases which makes mortality rate 0%, although endometritis and deep venous thrombosis occurred in one case [312].

Fetal Outcome

The fetus survived in 9/11 cases [313, 331] making fetal mortality rate of 18%. Fetal morbidity is unknown.

7.10.2 Congenital Defects

7.10.2.1 Sigmoid Mesocolon Hernia

Incidence

Sigmoid mesocolon hernia is an uncommon type and estimated to account for approximately 6% of an internal hernia [333, 334]. Up to 2005, there were 15 cases of transmesosigmoid hernias in general population (see Sect. Classification) [334]. There are only two cases in pregnancy and postpartum published (see Sect. Etiology).

Classification

Benson and Killen in 1964 classified these hernias in general population into three types [335]:

- *Intersigmoid hernia*: Herniation into an intersigmoid fossa, at the attachment of the lateral aspect of the sigmoid mesocolon
- *Transmesosigmoid hernia*: Incarceration of intestinal loops through an isolated, oval defect in the sigmoid mesocolon
- *Intramesosigmoid hernia*: A congenital, oval defect unrelated to the intersigmoid fossa, present in the lateral peritoneal surface of the mesocolon

Etiology

Pathologic apertures of the mesentery and visceral peritoneum are due mostly to congenital, surgical, traumatic, inflammatory, or circulatory etiologies [333]. Congenital causes of sigmoid mesocolon hernias have also been proposed as possible causes [334]. However, the role of congenital factors remains obscure and theoretical. Some case reports have documented transmesosigmoid hernias developing during pregnancy or postpartum [334, 336]. The authors proposed that dilatation and shrinkage of the uterus concomitant with pregnancy or delivery contributed to the development of transmesosigmoid hernias. The abnormal aperture could have been formed from the sigmoid mesocolon tearing by traction due to postpartum shrinkage of the enlarged uterus. One of the theories is that herniation could have occurred a few decades later through the abnormal aperture formed during the pregnant period in some cases.

Clinical Presentation

The clinical features of an internal hernia are abdominal pain, distention, and vomiting. Most patients complain of left lower abdominal pain.

Diagnosis

Plain abdominal X-ray shows distended small bowel loops and air–liquid level formation, suggestive of a mechanical obstruction.

The key CT findings for diagnosis of the transmesosigmoid hernia include [337]:

- A cluster of dilated fluid-filled loops of the small bowel entrapped in the left posterior and lateral aspect of the sigmoid colon through a mesosigmoid defect.
- The defect located between the sigmoid colon and the left psoas muscle.
- The sigmoid colon shows anterior and medial displacement.
- Encapsulated loops of the small bowel showed U- or C-shaped configurations and wall thickening representing closed-loop obstruction and ischemic change.
- Attached mesentery with vessels engorgement and fat obliteration indicating strangulation.
- The proximal small bowel shows dilatation.

However, in the majority of cases, the diagnosis of transmesosigmoid hernia is confirmed only by surgical intervention in general population [338].

An internal hernia can be precisely defined by abdominal MRI. In most cases, it is difficult to find the cause of obstruction in patients without previous surgery. Sometimes even precise location can be found and defined (Fig. 7.52).

Treatment

Patients with small bowel obstruction not responding to conservative management require an operation. If an internal hernia is suspected, the operation should be prompt, as strangulation and gangrene of the bowel are likely to occur if the surgery is delayed. The role of laparoscopy in patients with intestinal obstruction is being increasingly recognized in general population, but due to a small number of pregnant patients, its role in pregnancy is not defined. The necrosis of the strangulated intestine occurs in up to 80% of patients with a transmesosigmoid hernia during the course of treatment, necessitating extensive resection of the small intestine [340].

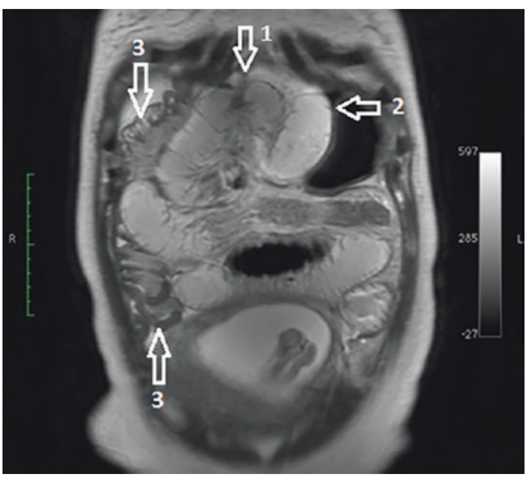

Fig. 7.52 Abdominal MRI showing the region of herniation: *1* site of herniation, *2* dilated intestinal loop, and *3* collapsed intestinal loop. Reproduced with permission from [339]

Prognosis

The maternal outcome is excellent because in both cases, there were no massive bowel resections, and the pregnant population is mostly young and without comorbidities.

7.10.2.2 Transomental Hernia

Idiopathic transomental herniation in general population is an extremely rare cause of small bowel obstruction, accounting for just 1–4% of all cases of intra-abdominal herniation [341]. There is only one case published during pregnancy with the confusing intraoperative description, different to one found in the title of the article (*There was a hernia sac between the root of the mesentery and transverse mesocolon*). The patient was discharged on the fifth postoperative day with a continuing pregnancy. She went into labor at term, had a labor epidural, and was delivered by emergency CS for suboptimal cardiotocography. A good-sized healthy female baby was born [342].

7.10.2.3 Falciform Ligament Hernia

A hernia through the falciform ligament is very rare and accounts for 0.2% of internal hernias, and most of them are asymptomatic. Theoretically, the incidence in comparison to general population could be increased due to physiologic increase in intra-abdominal pressure increasing the possibility of a (incarcerated) internal hernia. A congenital etiology for these defects is rare, attributable to malformation and incomplete development of the falciform ligament. There are two cases in pregnancy. One case in 20 weeks

pregnancy is published with the classic clinical presentation of small bowel obstruction. Falciform ligament should be divided by the open or laparoscopic approach. The division should be performed when small bowel is vital or gangrenous. Division prevents future herniation. Both published cases delivered healthy babies by CS [339, 343].

7.11 Gastric Outlet Obstruction

7.11.1 Heterotopic Pancreas

7.11.1.1 Incidence

Heterotopic pancreas (HP) in general population is often found incidentally in patients operated on for other reasons or during autopsies. The condition is relatively uncommon; it has been found in 0.6–13% of patients in autopsy studies [344, 345] and encountered in about one of 500 operations in the upper abdomen [346–348]. A few cases of HP as a cause of gastric outlet obstruction in infants, children, and adults [344, 349, 350] have been published.

There is one case of gastric outlet obstruction in pregnancy due to HP [73] and another case due to active chronic peptic ulcer [351].

7.11.1.2 Embryology

It is possible that early in fetal life, during rotation of the foregut and fusion of the dorsal and ventral parts of the pancreas, small parts are separated from it and continue to develop in the wrong location. Most often, HP is found in the stomach, duodenum, and jejunum, but it may also be found anywhere in the digestive tract, intra-abdominally, in the mediastinum, and in the lung.

7.11.1.3 Clinical Presentation

The symptoms can be (a) nonemergent such as epigastric pain (77%) and abdominal fullness (30%), (b) semi-urgent as tarry stools (24%) due to ulceration, or (c) emergent as due to intussusception and obstruction [346, 352]. Gastric outlet obstruction mostly presents first as postprandial vomiting and weight loss with the progression of vomiting [349, 350]. Although HP often exists from childhood, it seldom causes symptoms. Conditions that trigger this previously asymptomatic disorder to become symptomatic include bacterial infection and pancreatitis causing pancreatic edema [353, 354], and there is only one report of an ectopic pancreas becoming symptomatic due to pregnancy [73]. The cause of the symptoms could be due to the enlarging uterus that narrowed both the gastroduodenal canal and the peritoneal space, although the ectopic pancreas itself existed beforehand. Currently, there is no report about the relationship of enlargement of an HP due to the hormonal changes in gestation.

7.11.1.4 Diagnosis

This disorder is difficult to diagnose preoperatively, despite modern diagnostic procedures such as abdominal ultrasonography, esophagogastroduodenoscopy (Fig. 7.53), and contrast-enhanced abdominal CT [352]. According to one report of patients in general population, only 6% (1/17) of them were considered to have an HP preoperatively [352]. In the only published case in pregnancy [73], an accurate diagnosis was not able to be made from the abdominal MRI findings because of the contrast medium restrictions and the motion

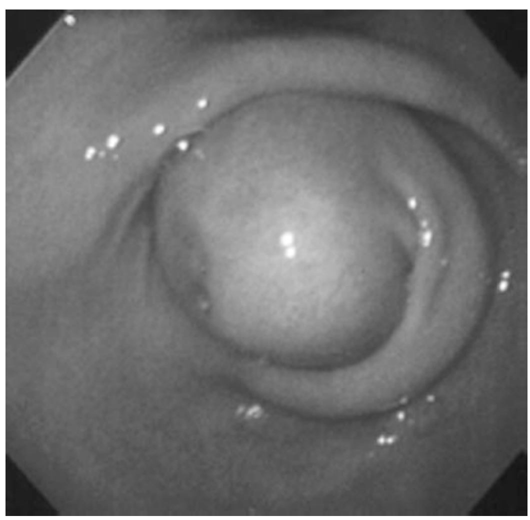

Fig. 7.53 Preoperative gastroscopy showing a submucosal tumor prolapsing through the pyloric ring and obstructing the gastric outlet. Reproduced with permission from [73]

Fig. 7.54 T2-weighted MRI showing a 4.7 × 3.6 × 2.4 cm target-like tumor in the posterior wall of the gastric antrum (*arrowhead*). The relatively large central portion showed a high signal intensity suggesting cystic components. The fetus can be clearly seen in the low abdomen. Reproduced with permission from [73]

artifact of the fetus (Fig. 7.54). Degenerated GIST is similar to a submucosal tumor with a central cyst, although it usually grows extraluminally in the upper stomach. In conclusion, HP should be considered in the differential diagnosis of a potentially obstructive gastric submucosal tumor, even though it is a rare event.

7.11.1.5 Treatment

There are two standard procedures for gastric outlet obstruction. One is endoscopic balloon dilatation (especially suitable for peptic gastric outlet obstruction) and another is surgery. Surgery is always indicated when there is a suspicion of malignancy. Full-thickness biopsy of the lesion at surgery is mandatory for establishing the diagnosis of HP from a frozen section; however, this carries the risk of scattering cells if there is a malignant disease [347]. This disorder can be treated by various operative procedures, including bypass gastroenterostomy or antrectomy with gastroduodenal anastomosis [347, 348]. Lymphadenectomy is not considered necessary as lymphatic spread rarely occurs from an HP or GIST [355]. Less invasive surgery can successfully be performed through a small skin incision. Antrectomy without lymph node dissection was most appropriate to avoid interruption of the pregnancy.

Histologically, HP with mucus retention of the gastric antrum needs to be differentiated from duplication and, although rare, mucinous adenocarcinoma arising from the ectopic gastric pancreas [356]. Frozen sections at surgery are not enough to distinguish these three diseases without verifiable pancreatic tissue [357]. Duplication of the stomach can easily be ruled out if the lining of the cysts did not consist of the normal gastric mucosa.

7.12 Gynecologic Causes

The cause of the intestinal obstruction is very important because apart from treating obstruction with its consequences itself, also a cause itself sometimes should be treated additionally. Gynecologic causes of the acute abdomen are present in the separate chapter, and gynecologic conditions would unlikely be considered as an underlying cause of intestinal obstruction.

7.12.1 Ovarian Teratoma

7.12.1.1 Incidence

The occurrence of teratoma with pregnancy is uncommon; only about 10% of the cases of matured cystic teratoma is diagnosed during pregnancy [358]. The most of the cases presented in the second trimester [359, 360]. Mature cystic teratomas usually occur in young women with a peak age incidence ranging 20–40 years [361].

7.12.1.2 Clinical Presentation

The most frequent symptom of teratoma is lower abdominal pain, and only few cases present for the first time with an abdominal mass. Though the complications of teratoma in pregnancy include torsion, rupture, and obstruction to the birth canal, there is only one reported case of its association with intestinal obstruction [359]. There was a 2-week history of abdominal pain, abdominal distention, and vomiting. The pain was located in the umbilical region and was col-

icky in nature. There was associated constipation with signs of generalized abdominal tenderness.

7.12.1.3 Diagnosis

With respect to diagnosis, abdominal ultrasound (transabdominal and transvaginal) scan is the method of choice. In the single case report, a repeat ultrasound scan also reported a singleton intrauterine pregnancy with vague abdominal masses on both sides of the uterus and distended bowel loops. It is able to determine the dimension of the tumor [359].

7.12.1.4 Treatment

A diagnosis of intestinal obstruction in pregnancy was made, and a laparotomy was performed. Findings at surgery were those of bilateral ovarian masses (benign cystic teratoma) with the right causing kinking of the small intestine (ileum). The right mass adhered partially to the ileum, and it separated from it without difficulty (Fig. 7.55). The adhesion might have resulted from a response of the surrounding tissue, including intestine to the pressure effect of the tumor. On the other hand, it might have also resulted from a minor leak of tumor content into the surrounding tissue. However, there was no evidence of invasion of the intestinal wall thus ruling out gross feature of malignancy. The size of both tumors was approximately 15 cm in diameter. This tumor possibly existed before the onset of pregnancy.

> The teratomas less than 6 cm occurring before pregnancy do not grow during pregnancy [362].

7.12.1.5 Prognosis

As the tumor was benign, the pregnancy was carried to term, and she delivered a male baby by spontaneous vertex delivery with Apgar score 7 at 1 min and 8 at 5 min [359].

7.12.2 Ectopic Pregnancy

7.12.2.1 Incidence

Most complications of ectopic pregnancy are in the form of tubal rupture with massive hemorrhage and hemorrhagic shock. There are only three cases of intestinal obstruction due to ectopic

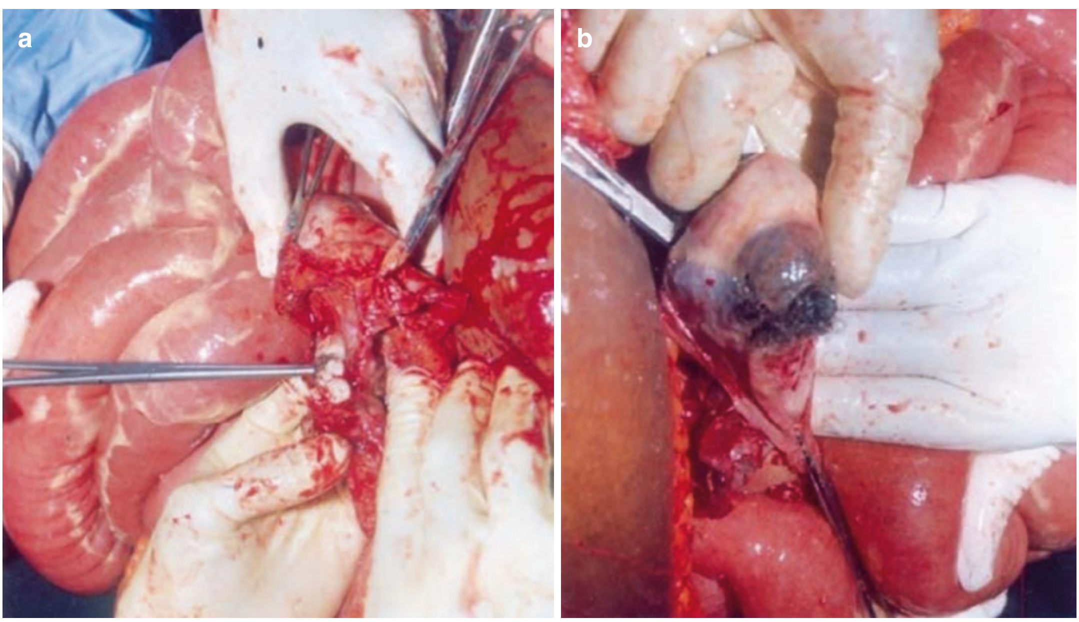

Fig. 7.55 (**a**) Teeth and other structures of benign ovarian teratoma causing small bowel obstruction with dilated loops; (**b**) intra-abdominal teratoma being teased from distended bowel loops. Reproduced with permission from [359]

pregnancy published. In the majority of cases, terminal ileum was the level of obstruction [363–365].

7.12.2.2 Clinical Presentation

Rarely intestinal obstruction and ectopic pregnancy can present simultaneously. The most common signs and symptoms of ectopic pregnancy include amenorrhea, abdominal pain, irregular vaginal bleeding, and pain on abdominal or pelvic examination. A pelvic adnexal mass is palpated in only 50% of the patients. Unfortunately, the most common signs and symptoms of ectopic pregnancy are correct in predicting only 50% of cases [366]. Abdominal pain is the single most consistent feature of ectopic pregnancy [367] but can be masked due to other symptoms of intestinal obstruction. Clinicians should have a high index of suspicion for ectopic pregnancy in patients with a previous history of tubal pregnancy, tubal surgery, pelvic inflammatory disease (PID), tubal disease, endometriosis, abdominal surgery itself, intrauterine device, fertility treatment, smoking, and history of multiple sexual partners. The presentation of bowel obstruction is described earlier in the chapter (see Sect. 7.1).

7.12.2.3 Differential Diagnosis

Differential diagnosis of intestinal obstruction due to ectopic pregnancy includes all possible causes of intestinal obstruction. One of the common confusions is growing uterine fibroid in pregnancy causing compression on the bowel.

7.12.2.4 Diagnosis

Increased chances of correct diagnosis of an ectopic pregnancy are possible with accurate menstrual and sexual history and availability of serum βHCG measurement and transvaginal ultrasound (see. Chap. 15). Transabdominal ultrasound is of little help due to dilated bowel loops which prevent adequate visualization. The diagnosis of bowel obstruction is described earlier in the chapter, and the diagnostic algorithm is standard when an intestinal obstruction is suspected. These diagnostic modalities itself cannot reveal ectopic pregnancy as the cause of obstruction. First, diagnostic modality is plain abdominal X-ray showing air–liquid levels indicating small or large bowel obstruction [364]. Almost all ectopic pregnancies are tubal (97.7%); therefore, obstruction develops in the lower abdomen, and two of three cases were located in the terminal ileum.

7.12.2.5 Treatment

There are several therapeutic options for ectopic pregnancy per se, including medical, expectant, and surgical (see Chap. 15). In cases with intestinal obstruction due to ectopic pregnancy, surgery is the only modality to deal with intestinal obstruction and ectopic pregnancy simultaneously.

Surgical Treatment

The type of operation for intestinal obstruction depends on the severity of the obstruction. If simple, adhesiolysis is performed. If gangrene is present due to long-standing obstruction or strangulation, bowel resection is made. A decision on continuity or stoma is made on several factors as in other causes of intestinal obstruction.

Gynecologic Treatment

The type of operation for ectopic pregnancy depends on the location of ectopic pregnancy. Treatment of choice for unruptured ectopic pregnancy is salpingostomy, sparing the affected Fallopian tube and thereby improving future reproductive outcome. Salpingectomy is performed if Fallopian tube is morphologically changed in a way that it precludes further fertility (see Chap. 15).

7.12.3 Normal Pregnancy

7.12.3.1 Historical Perspective

Pinard in 1902 was quoted by LePage et al.: *There is no need to begin another chapter in puerperal pathology entitled "Intestinal Occlusion of Pregnancy". I have never seen intestinal occlusion complicate a normal pregnancy* [368]. The explanations offered by the various French and German writers varied. The French writers discuss the anatomic causes in

abdomens without previous surgical intervention and so without adhesions as far as is known. Sencert and Cuneo called attention to the intestinal occlusion caused by a loop of bowel caught and held by the infundibulopelvic ligament, the latter being held taut by a gravid uterus rising into the abdomen. Vautrin, of Nancy, in 1922 presented two cases of acute intestinal obstruction caused apparently by normal pregnancy [368]. Vautrin pointed out the "colic angulation" caused by the tense infundibulopelvic ligament, the stercoral accumulation adding to the trouble, and the two causing obstruction. Ludwig, in 1913, assembled 96 cases of intestinal obstruction occurring during pregnancy. He found the condition most common in the third and fourth months and again in the last 3 weeks of pregnancy [2]. These cases were perhaps in part aggravated by the pregnancy, but none could be directly attributed to the pregnancy alone. In 1918, Fleischauer [368] reported two intestinal obstructions during pregnancy—one, a woman pregnant 4 months, with severe obstruction and peritonitis. At the autopsy, a hindrance to the passage of the intestinal contents was found at a point where the possibility of compression between the uterus and pelvic brim arose. There was also dilatation of the ureters where they entered the pelvis, so that in this case the gravid uterus must be considered the cause of the obstruction, in his opinion. According to Fleischauer, this case confirmed the opinion of van der Hoeven, in 1912, that in the third and fourth months of pregnancy, an occlusion of bowel is more liable to appear than at any other time, that is to say, at the time the uterus rises beyond the brim of the pelvis [368]. Der Verf was of the opinion that in the final analysis the cause of the ileus is to be found in the bowel itself owing to muscle weakness and loss of muscle tone. A second case, by Fleischauer, appeared at the sixth month. The obstruction was caused by adhesions from a previous operation—the growing uterus being simply the deciding factor in the cause of the ileus. In LePage et al.'s comprehensive treatise on the subject from 1913, the patients are divided into two classes [368]:

- Without any past history of intestinal or peritoneal trouble
- With history of intestinal or peritoneal trouble and possible operation

LePage et al. say: *If we can diagnose those exceptional cases in which the presence of a gravid uterus suffices to produce obstruction, even occlusion, in an intestine non-adherent and with no bands, but simply compressed, therapeutics should immediately consist in getting rid of the uterine tumor*. This course, he adds, *raises the great question of the right of the fetus to life*. Köhler, in 1920, says the cases in which a pregnant uterus alone produces the ileus are rare [369].

7.12.3.2 Incidence

The incidence is extremely rare. Review of the literature up to 1926 by Bohler found only 12 cases published in a paper from 1930 [369].

7.12.3.3 Pathophysiology

The concept of pathophysiologic process is simple. The enlarged uterus causes compression, on the locations where the bowel cannot move freely or where there are junctions of mobile and immobile parts of the bowel:

1. Rectosigmoid junction (pelvic brim)
2. Point where the bowel, in a form of a stoma, enters the abdominal wall
3. Ileum proximal to the ileoanal pouch (J-pouch)

1. Rectosigmoid junction is the most common location because the uterus is located in the lower abdomen in all phases of uterine enlargement. The possible additional factor is long sigmoid loop predisposing to kinking and development of sharp angles [370–372].
2. Theoretically, the incidence is increasing as the pregnancy advances due to enlargement of the uterus (both cases are after 32 weeks of gestation). In pregnant patients with the normal bowel anatomy, the terminal ileal loops remain relatively mobile, allowing them to

move aside when abutted by the enlarging uterus and thereby maintain normal patency and function. The obstruction can have several similar mechanical mechanisms. The enlarging uterus may in addition drag on the ileostomy loop from within, causing stomal retraction. Incarceration is a theoretical risk; it can arise either from adhesions fixing the retroverted uterus in the pelvis or possibly from the pernicious habit of rectal surgeons of using the uterus to close the pelvic floor after excision of the rectum. Stomal problems are common and are caused by displacement, enlargement, and sometimes prolapse. Fortunately, most of the stretching of the abdominal wall is in the region of the linea alba, and the stoma gets eased out of the way laterally. It should be noted that in patients with an ileostomy, additional nutritional support, as oral iron, can provoke ileostomy dysfunction.

3. The explanation could be that ileum proximal to J-pouch is more or less tensed and cannot freely move away from the enlarging uterus, and therefore obstruction occurs (see Sect. 8.2.1).

There are some conditions that should be fulfilled for the diagnosis of *intestinal obstruction caused by normal pregnancy*:

- No obstructive symptoms before pregnancy except long-standing constipation
- No other causes of obstruction intraoperatively
- Compression of the enlarged uterus on the bowel at the site where the proximal distended bowel continues to the collapsed bowel
- No other causes of stomal obstruction (a parastomal hernia, stenosis, or prolapse)

7.12.3.4 Diagnosis

When the intestinal obstruction is suspected, of any cause, plain abdominal X-ray is most often diagnostic and sufficient for the indication for the emergent operation. MRI of the abdomen (with or without peroral contrast) can be used in unequivocal cases (Fig. 7.56). Multiplanar images could demonstrate multiple loops of the dilated small

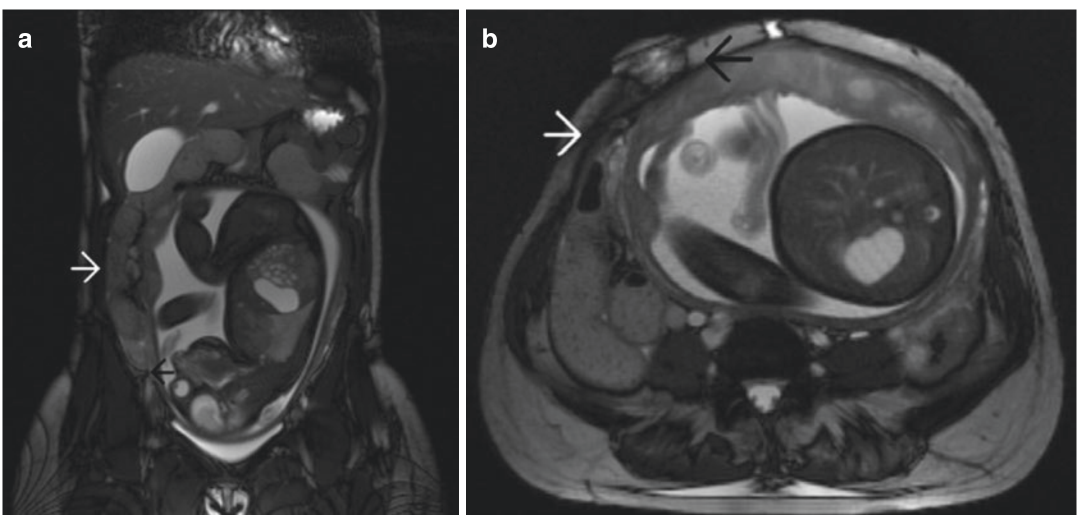

Fig. 7.56 (**a**) Coronal T2-weighted MRI identifies dilated loops of the small bowel (*white arrow*) from the left upper quadrant down to the level of the ileostomy in the right iliac fossa (*black arrow*). (**b**) Axial MRI at the level of the stoma identifies a change in caliber, (*white arrow*) from the dilated small bowel to the collapsed bowel adjacent to the uterus indicating the compressive effect of the uterus to be the cause of obstruction. Reproduced with permission from [261]

intestine. The point of transition from distended to the collapsed bowel can be identified with or without focal lesion as they likely cause of obstruction. MRI is important because it can delineate bowel wall thickening or mucosal abnormalities or signs of a parastomal hernia [261].

7.12.3.5 Treatment

It is fortunate that the condition is extremely rare, and when it does occur, the majority of babies have reached the age of viability. It would seem sane to suggest, then, that when intestinal obstruction intervenes in the course of normal intrauterine pregnancy, the abdomen be opened and the cause, if at all possible, be ascertained. If there are no causes of obstruction except bowel compression by the enlarged uterus, then CS should be performed. If there is a suspicion that intestinal obstruction is due to pregnancy, without strangulation, and is present near term, the delivery should be started, vaginally or by CS [372]. If the pregnancy is less than 28 weeks, in many instances, this obstruction is relieved by placing the patient in the knee–chest position and by dislodging the uterus by rectal manipulation.

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8 Acute Inflammatory Bowel Disease

Abstract

The incidence of inflammatory bowel disease is rising in general population, especially in adolescence and early adulthood, and consequently, it is rising in pregnant population. Interestingly the severity and progression of the disease depend on the disease activity during pregnancy. Therefore, it is mandatory to have a patient in a remission before planned pregnancy for minimization of the possibility of the disease progression and complications during pregnancy. When inflammatory bowel disease during pregnancy is active, an additional problem is the use of immunomodulatory and biologic agents which can influence fetal development. On the other hand, prolonged infection during pregnancy increases the rate of preterm labor, fetus small for gestational age, and other obstetric complications. An additional problem is pouch surgery before and during pregnancy because functional results can be lower due to the compression of growing uterus. Also, type of delivery could be influenced by the pouch surgery and pouch function at the time of delivery.

8.1 Crohn's Disease

8.1.1 Introduction

Crohn's disease (CD) was first seen by German surgeon Wilhelm Fabry, also known as William Fabry, Guilelmus Fabricius Hildanus, or Fabricius von Hilden (Fig. 16.1) in 1623 [1], and was later described by and named after the US physician Burrill Bernard Crohn [2]. In general population, the incidence of CD in Western countries increased markedly between the 1950s and the 1980s [3, 4]. Since the 1980s the incidence has continued to increase at a rather slower rate [5, 6]. The incidence of inflammatory bowel disease (IBD) has a bimodal distribution curve with the greater peak in younger patients: 50% of patients are younger than 35 years old at the time of diagnosis [7], and 25% conceive for the first time after their diagnosis of IBD [7–9]. This age range corresponds to female reproductive age and increases the likelihood of CD during pregnancy.

The first presentation of intestinal obstruction (with the abscess) due to CD during pregnancy was described by Babson in 1946 [10].

8.1.2 Effect of Pregnancy

8.1.2.1 Pregnancy-Related Changes of Maternal Immune System and Fibrous Tissue

Failure of maternal rejection of the fetus, which is effectively a foreign allograft, is evidence that the maternal immune system may be modified. While the etiology for this is not understood, a possible factor inducing quiescent disease may be a disparity in HLA class II antigens between mother and fetus, suggesting that the maternal immune

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_8

response to paternal HLA antigens may result in immunosuppression that affects maternal immune-mediated disease. This has been demonstrated in rheumatoid arthritis [11] as well as in IBD [12]. Increased laxity of fibrous tissues, partly due to the hormone relaxin, an insulin-like peptide produced by the corpus luteum of pregnancy, results in dissolved and disorganized collagen fibers [13]. These pregnancy-induced effects on the immune system and fibrous tissue could affect the bowel in CD: reduce the chronic inflammatory response, reduce fibrous tissue formation, and thus reduce the frequency of stenosis and resection rates [12, 14]. The increasing parity reduces the need for further surgical resections which is confirming this immunoprotective role of pregnancy [15].

A history of pregnancy at the time of diagnosis is a favorable prognostic indicator in both distal ileal and colonic CD. These results should be taken with caution because severely ill patients with CD could have impaired fertility or no desire for children at that time. The comparative resection data suggest, however, that even patients who had been pregnant by the time of diagnosis of their CD need fewer surgical resections subsequently. In addition, multiple perioperative blood transfusions may decrease recurrence in CD by decreasing immune responsiveness [16].

8.1.2.2 Disease Activity During Pregnancy

Crohn et al. in 1956 suggested that if the onset of the disease occurs during pregnancy, then its subsequent course is severe and relapsing [17]. This view was later challenged with the suggestion that CD activity is unaffected by pregnancy [18] and that the activity of CD during pregnancy reflects the disease activity at the time of conception [19]. Measurement of CD activity, however, as a single-point assessment in a lifelong disease is an incomplete measure of long-term outcome. Sixty years ago, pregnant patients with CD (originally with IBD) were classified in four categories [17, 20]:

- Inactive at conception
- Active at conception
- Arising during gestation
- Arising during the puerperium

There are two factors responsible for higher remission rate and lower disease activity (decrease in the Harvey-Bradshaw index) during pregnancy [21]. The influence of pregnancy on CD is explicable by the increased steroid production during pregnancy and the falloff during the puerperium. The amelioration of symptoms followed by relapse during the puerperium would thus be the natural consequence. In previous decades, others claimed that 25% of patients have the worsening of the baseline CD activity during the postpartum period, attributed to the sudden decrease in endogenous corticosteroids after delivery [22]. Reduced disease activity in pregnancy is partly due to reduced tobacco smoking during pregnancy [23]. Smoking has a known negative effect on the course of CD [21]. It is interesting that there is a higher incidence of smokers among pregnant IBD patients in quiescent phase (43%) than normal pregnant women (14%), but due to a small number of patients, the difference was not significant [24].

Approximately one-third of women with inactive IBD at conception will relapse during the pregnancy [24–27], most commonly in the first trimester [28]. Exacerbations of disease in the first trimester of pregnancy are often due to discontinuation of maintenance therapy [29]. This risk of a flare (19–26%) is no greater than any other year of the patient's life [30–33]. The only significant risk factor for disease relapse is a longer duration of disease [30]. There are comparable postpartum flare rates in breastfeeding (26%) versus not breastfeeding (29.4%) IBD mothers [34]. Discontinuation of therapy while breastfeeding could be one of the determinants of the higher flare rate [35].

If conception occurs at a time when IBD is active, 60–70% continue to have active disease during the pregnancy despite medical therapy [30, 36–38]. One-quarter of patients with active IBD during pregnancy will experience chronically active disease and in about half of these patients, the disease will worsen (45% UC, 33% CD) [39]. The active disease has been associated with miscarriage, stillbirth, prematurity, and low birth weight (LBW) [40].

Thus, conception is advised when IBD is in remission. There is a decrease in relapse rate in CD patients 4 years after pregnancy, in comparison with the 3 years before pregnancy [41]. The rates of CD relapse decreased in the years following pregnancy in comparison to prepregnancy (0.76 vs. 0.12 flares/year) [42]. Disease progression within 2 years after childbirth is significantly more frequent in those patients with the active luminal disease compared to women with inactive luminal disease prior to pregnancy, and this was independent of the mode of childbirth [25]. Patients with CD who were pregnant during the course of their disease did not have higher rates of stenosis (37% vs. 52%) or resection (0.52 vs. 0.66).

There is no evidence that the patients developing symptoms for the first time during pregnancy experience unusually severe disease. Severe exacerbations of CD in pregnancy are rare. Even less common are acute manifestations that require surgery [17, 37, 43, 44].

Classification

All patients should have their disease phenotype classified in accordance with the *revised Montreal classification* (Table 8.1). Classification attempts to more accurately characterize the clinical patterns of CD [45, 46]. In addition, it could serve for better understanding of the disease dynamics during pregnancy, treatment options comparison, and finally prognosis.

Table 8.1 Definition of Crohn's disease phenotype according to the Montreal classification

Age of onset	Location	Behavior
16 years (A1)	Ileal (L1)	Non-stricturing, non-penetrating (B1)
17–40 years (A2)	Colonic (L2)	Stricturing (B2)
>40 years (A3)	Ileo-colonic (L3)	Penetrating (B3)
	[a]Isolated upper GI disease (L4)	+ "p" if perianal disease

[a]L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal (GI) disease is present
Reproduced with permission from [45]

8.1.2.3 Pregnancy and Surgical Therapy for CD

Parity (before and after the diagnosis of CD) and surgical resections are associated in patients with distal ileal and colonic CD [15]. Increasing parity reduces the need for further surgical resections. The subgroup analysis suggests that this trend is present even in patients who became pregnant after the diagnosis of CD was made. These results might be explained by severely ill patients with CD having impaired fertility or no desire for children at that time. The comparative resection data suggest, however, that even patients who had been pregnant by the time of diagnosis of their CD need fewer surgical resections subsequently. The number of resections/patient is lower in the parous patients, and a history of pregnancy at the time of diagnosis of CD is associated with a longer interval between the first and second resection. A larger proportion of patients in the parous groups had either no or only one resection compared with patients in the resection group. The differences could reflect changing surgical practice during almost four decades [15].

8.1.3 Pathophysiology

8.1.3.1 Free Intestinal Perforation

There are several possible mechanisms that may account for free perforation of CD during pregnancy. Either an abscess adjacent to the CD's segment ruptures by the mechanical stress of labor or there is a failure of the intra-abdominal viscera to "wall-off inflamed segments." In the latter case, the large uterus may prevent the greater omentum and other abdominal contents from adequately localizing the inflammation (see Chap. 1). Even the avulsion of the ileal wall by the rapid retraction of the uterus in the postpartum period was described as the probable pathogenesis of an ileal perforation in the case of exacerbation of CD in pregnancy [47]. This should be taken into account when considering the opportunity and dosages of postpartum uterotonics in these patients.

8.1.4 Clinical Presentation

8.1.4.1 Elective Presentation

Most patients have symptoms and diagnosis of CD prior to pregnancy. CD presenting for the first time during pregnancy is very rare. Diagnosis of new onset of CD in pregnancy is very difficult and requires a high degree of suspicion because the symptoms are often nonspecific and are similar to symptoms common to normal pregnancy or hyperemesis gravidarum. The symptoms of CD depend on (1) the disease location in the digestive tract and (2) the severity. The most common symptoms of CD in both pregnant and nonpregnant women are diarrhea, whether bloody or nonbloody, abdominal pain, fever, feeling of a mass or fullness in the lower, right abdomen, and weakness. Pregnant women often present insufficient weight gain that may be related to malabsorption or to decreased intake since patients with obstructing segments of bowel feel better when they do not eat. Additional symptoms of the acute abdomen during pregnancy are related to the underlying pathophysiologic process: intestinal obstruction, intraluminal bleeding, and bowel perforation.

Physical examination may be normal or show nonspecific signs (pallor, weight loss). In addition, findings suggestive of the extraintestinal manifestations of IBD could be found and therefore should be searched for (see Sect. 8.2.5.1). Proctologic conditions such as anal fissure, perianal fistula, and abscess are particularly associated with CD. Glossitis and aphthous ulcers in the mouth and beaking or frank clubbing of the nails are common.

8.1.4.2 Emergent Presentation

Intestinal Perforation

Free intestinal perforation presents as acute abdominal pain with signs of peritonism. Depending on the pathophysiologic mechanism responsible for the perforation clinical presentation can defer. If perforation due to obstruction is the cause, then symptoms and signs of intestinal obstruction (see next paragraph) are present before peritoneal signs (peritonitis). If the perforation is due to progressive inflammation of bowel wall, then the abdominal pain of lesser intensity with possible mucus and diarrhea (with or without blood) can precede signs of peritonitis.

Intestinal Obstruction

Abdominal distention, nausea, vomiting, and crampy abdominal pain in the early stages are the leading symptoms. This initial phase can be accompanied with diarrhea and fever, sometimes misleading the clinician to gastroenterocolitis. This symptomatology can be present earlier in pregnancy or even before pregnancy [10]. Later in the course of the disease, pain is constant, and there is no passage of stool or flatus. Also, CD patients are prone to partial bowel obstruction when the crampy abdominal pain or vomiting is related to larger meals or even every meal.

Intestinal Stomal Obstruction

See Sect. 7.7.

Presentation Mimicking Acute Appendicitis

The patient can present with right lower quadrant pain mimicking acute appendicitis (see Sect. 1.5). It is important to note symptoms before this acute presentation in form of previous episodes of (crampy) abdominal pain, diarrhea, or loss of weight, which were not present if this is the first attack of CD. The clinical differentiation is sometimes difficult in general population, while presentation in pregnancy adds more difficulty in defining the diagnosis.

8.1.5 Diagnosis

8.1.5.1 Laboratory Findings

Diagnostic procedures are no different from usual during pregnancy. Interpretation of blood investigations for IBD during pregnancy can be difficult. Due to hemodilution, hemoglobin and albumin decrease as pregnancy progresses, and therefore they cannot be used in the assessment of disease activity. Iron deficiency is common because of chronic iron loss, and this may be

exacerbated during pregnancy; thus, a *hypochromic, microcytic anemia* is frequently present. Laboratory investigations should include full blood count, urea and electrolytes (potassium, sodium, calcium, and magnesium), liver function tests and erythrocyte sedimentation rate or C-reactive protein (CRP), ferritin, transferrin saturation, vitamin B12, folate, and albumin.

Leukocytosis (raised white blood cell count—WBC) is not diagnostic as this can go up in the second and third trimesters and can reach 20,000/mm^3 in early labor in normal pregnancy [48]. In view of the wide range of values, however, it is not possible to derive clinical relevance from these data. *Neutrophil granulocytosis with left shift*: the presence of increased proportions of younger, less well-differentiated neutrophils and neutrophil precursor cells in the blood is diagnostic of acute (bacterial) infection.

CRP levels remain relatively stable (<10 mg/L) during pregnancy and can be used to assess disease activity [40] but should be interpreted with caution for the diagnosis of maternal infection in the postpartum period because it rises 10–20-fold in normal pregnancy but may be useful for diagnosing neonatal diseases [49]. CRP and serum amyloid A levels in mother's serum at the moment of a normal delivery are much higher than the levels found in cord blood. This finding reinforces the idea that there is a lack of transplacental transfer of these proteins during labor [49, 50]. Thus, any increase in the newborn CRP and serum amyloid A levels may be a sign of infection or trauma. On the contrary, the concentrations of TNF-α are higher in cord than in maternal blood. The concentration of TNF-α in cord blood may originate exclusively from fetal and placental tissues and may contribute to neonatal host defense [49, 51].

Patients with small bowel disease or ileal resections are at risk of folate or vitamin B12 malabsorption or with a macrocytosis should have levels of vitamin B12 and folate checked.

Fecal calprotectin is accurate in detecting colonic inflammation and can help identify functional diarrhea. All patients with diarrhea should be microbiologically tested for *C. difficile* toxin, in addition to standard organisms. A minimum of four stool samples is required to detect 90% of cases [52, 53].

Both osteoporosis and vitamin D deficiency (including compensated deficiency states with normal calcium and high parathyroid hormone) are common in CD. The major risk factors for osteoporosis complicating CD are age, steroid use, and CD activity.

8.1.5.2 Imaging Modalities

Standard radiological investigations for CD such as barium fluoroscopy and large bowel enemas and isotope-labeled white blood cell scans are contraindicated because of the radiation exposure to the fetus.

Transabdominal ultrasound cannot comprehensively assess the gut when used in isolation. It is the first-line test for gallstones and kidney stones, which should not be forgotten as complications of CD. In expert hands, it has a high sensitivity for detecting disease, particularly thickening of the wall of the terminal ileum or the presence of an intra-abdominal abscess. It can exclude or confirm acute appendicitis which is the most common differential diagnosis.

Both computer tomography enterography and magnetic resonance (MR) enterography are commonly used to evaluate disease activity and complications in CD patients in general population. Abdominal MRI is a safe noninvasive investigation in pregnancy and has been useful in establishing the diagnosis of CD [54]. MR enterography should be performed in classic abdominal; MR is not diagnostic. However, there is a paucity of data outlining the utilization of MR enterography in pregnant CD patients. In particular, safety data pertaining to the intravenous contrast material (gadolinium) routinely utilized in MR enterography is very limited, and its use in pregnancy is recommended only when absolutely necessary [55]. The typical radiographic signs of active CD include mural thickening of 3 mm or more, ulcers, wall edema, *comb sign*, phlegmon, abscess, and fistula (Fig. 8.1). This is a valuable method that can distinguish between CD and UC, and it is accurate in estimating disease severity. This is important especially in pregnancy for adjusting drug therapy.

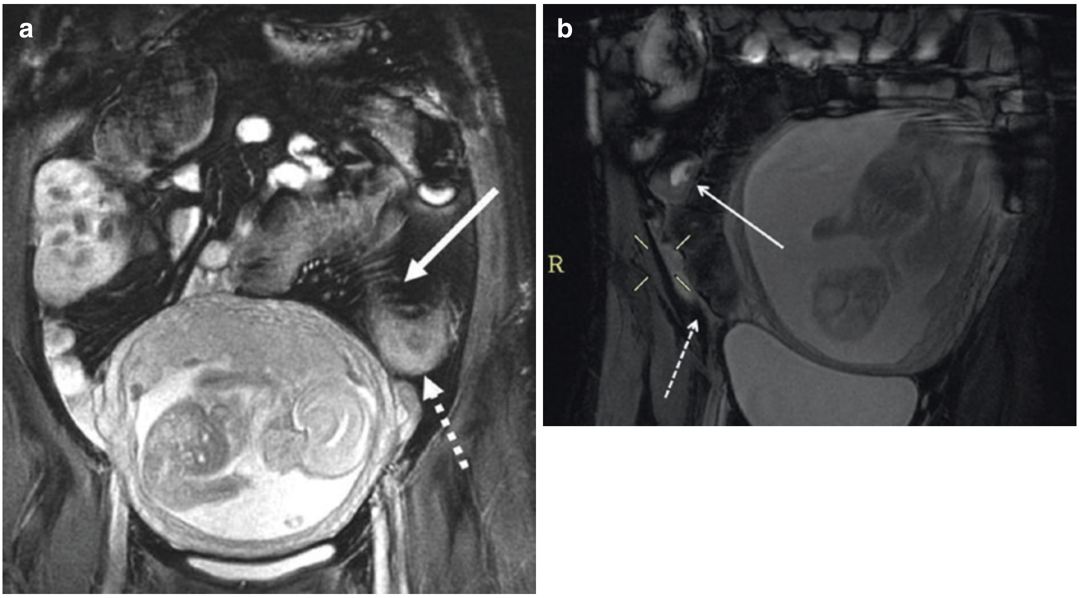

Fig. 8.1 (**a**) A 19-week pregnant patient with CD, Coronal FIESTA: signs of active disease—mesenteric congestion (*arrow*) and large bowel mural thickening and edema (*dotted arrow*). (**b**) A 20-week pregnant patient with CD, Coronal FIESTA: signs of active disease—small bowel mural thickening and ulcer (*arrow*), note free fluid (*dashed arrow*). Reproduced from [55] under the CC BY 4.0

8.1.5.3 Endoscopy

Recent reports confirm the safety of colonoscopy and flexible and rigid sigmoidoscopy in pregnant patients. Endoscopy does not induce labor or result in significant side effects to the mother or fetus and can be performed safely in medically stable pregnant patients [43, 56]. Colonoscopy with multiple biopsies (at least two biopsies from five sites including the distal ileum and rectum) is the first-line procedure for diagnosing colitis. It allows classification of disease based on the endoscopic extent, the severity of mucosal disease, and the histological features. It also allows assessment of suspected stenoses in the distal ileum or colon. Upper gastrointestinal endoscopy should be considered in coexisting dyspepsia.

8.1.6 Differential Diagnosis

8.1.6.1 Intestinal Obstruction

As in general IBD population, the most common causes of intestinal obstruction are adhesions, bowel inflammation with or without strictures, or bowel ischemia. In pregnancy compression by enlarged uterus during pregnancy can also be the cause (see Chap. 7).

8.1.6.2 Acute Appendicitis

The first presentation of ileocecal CD is difficult to distinguish from acute appendicitis, especially because sonographic findings could be similar, and clinicians are reluctant to use abdominal CT when acute appendicitis is suspected.

8.1.7 Treatment

8.1.7.1 Medical Treatment

Pharmacological therapy for CD during pregnancy is similar to pharmacological therapy for nonpregnant patients and patients maintained in remission by way of pharmacological therapy should continue it throughout their pregnancy, with few exceptions. Only 2.7% patients with UC and CD require surgical intervention; the rest are controlled with medical therapy alone [38]. It was reported that 48.6–77% were undergoing treatment at the time of conception and 46.9–65% continued medication throughout pregnancy

[30, 42]. The majority were receiving mesalamine or azathioprine [30].

Two important factors determine the management of a pregnancy in the presence of CD: the disease activity (quiescent vs. active) and when a flare-up occurs—before (fertility), during (early and late pregnancy), or after pregnancy (breastfeeding). Overall, the majority of medications used for the treatment of IBD are not associated with significant adverse effects (Table 8.2), and maintaining the health of the mother remains a priority in the management of these patients. Therefore, flares should be treated aggressively to prevent adverse outcomes.

The greatest risk to mother and fetus during pregnancy is active disease and not the medications used to treat it.

Antibiotics

There is no association between *metronidazole* treatment during all three trimesters of pregnancy and preterm birth, low birth weight, or congenital anomalies [60]. One population-based case–control study observed an increased incidence of cleft lip and/or cleft palate in infants of mothers exposed to metronidazole in the first trimester of

Table 8.2 Medications used in the treatment of inflammatory bowel disease [57–59]

Drug	FDA	Pregnancy	Breastfeeding
Adalimumab	B	Limited human data: low risk	No human data: probably compatible
Alendronate	C	Limited human data; animal data suggest risk	No human data: probably compatible
Ampicillin/clavulanic acid	B	Low risk	
Azathioprine/6-mercaptopurine	D	Transplant literature suggest low risk	No human data: potential toxicity
Balsalazide	B	Low risk	No human data: potential diarrhea
Budesonide	C	Data with inhaled drug low risk. No human data for oral drug	No human data
Cephalosporins	B		
Ciprofloxacin	C	Potential toxicity to cartilage	No human data: probably compatible
Corticosteroids	C	Low risk: cleft palate, adrenal insufficiency, premature rupture of membranes	Compatible
Cyclosporine	C	Low risk	Limited human data: potential toxicity
Etanercept			Excreted in milk—probably too large molecule for oral absorption
Fish oil supplements	–	Safe, possibly beneficial	No human data
Infliximab	B	Low risk: limited human data	Limited human data: probably compatible
Loperamide	B	Low risk	
Mesalamine (oral and topical)	B	Low risk	Limited human data: potential diarrhea
Methotrexate	X	Teratogenic	Contraindicated
Metronidazole	B	Limited efficacy in IBD—avoid in first trimester	Limited human data: potential toxicity
Olsalazine	C	Low risk	Limited human data: potential diarrhea
Risedronate	C	Limited human data	Unknown
Rifaximin	C	No human data: animal teratogen	Unknown
Sulfasalazine	B	Low risk. Give folate 2 mg daily	Limited human data: potential diarrhea
Sulfonamide	C	Not recommended	
Tacrolimus	C	Low risk	Limited human data: potential toxicity
Tetracycline	C	Not recommended	Not recommended
Thalidomide	X	Teratogenic	Limited human data: potential toxicity

Low risk is defined as "the human pregnancy data does not suggest a significant risk of embryo or fetal harm"

pregnancy [61]. Metronidazole use in pregnant IBD patients is best limited to short-term use for the treatment of pouchitis. Metronidazole is excreted in breast milk, and breastfeeding during metronidazole use is not recommended [62]. *Quinolone* antibiotics (FDA C) should be avoided because they carry an increased risk of arthropathy due to their high affinity for bone and cartilage. Data on breastfeeding are limited, but quinolone use is probably compatible with breastfeeding [63, 64].

Aminosalicylates (FDA B)

Sulfasalazine (500 mg/day to 6 g/day) consists of sulfapyridine linked to a salicylate radical by a diazo bond. When taken by mouth, only a limited amount is absorbed from the small intestine, and most of the drug reaches the colon intact. There it is split at the diazo bond by the colonic bacteria into sulfapyridine and 5-aminosalicylic acid (5-ASA). The sulfapyridine is virtually all absorbed and is then metabolized in the usual way of sulfonamides. Up to 3 g/day are allowed. The 5-ASA is only partly absorbed and is rapidly excreted in the urine so that the serum concentration is very low. Maintenance therapy with sulfasalazine throughout pregnancy and puerperium in patients with UC has no obvious ill effects on the mother or the child [65, 66]. Nevertheless, sulfasalazine and its metabolites reach the fetus in concentrations not greatly different from those in the maternal serum. There is, therefore, a theoretical risk that the fetus might develop complications from the treatment. Although sulfapyridine competes with bilirubin for the same albumin-binding site, there are no reports indicating a higher risk of kernicterus in newborns of mothers exposed to sulfasalazine [67, 68]. Sulfasalazine should be stopped if there is suspected neonatal hemolysis. *Mesalamine* proved safe during pregnancy in conventional (low) doses [69, 70] and even high doses [70, 71]. A few studies reported the risk of neonatal interstitial nephritis with higher doses of mesalazine (>3 g/day) [69, 71]. Mesalamine: 1 g orally four times a day. Mesalamine, delayed-release tablet: 500 mg orally twice a day. Mesalamine, enema: one application twice a day (once at bedtime and retained during sleep). Large doses of *olsalazine* (1.6 g orally three times a day) have been shown to cause birth defects in animals; it is not known whether olsalazine crosses the placenta to the fetus. The FDA has placed olsalazine in risk category C: the drug should be used during pregnancy only if its benefits clearly outweigh the potential risks. *Topical 5-ASA* has also proved to be safe and effective in the management of women with localized distal colitis/proctitis requiring treatment during pregnancy [72].

The concentrations of sulfasalazine, salazopyrine, and other aminosalicylates and its metabolites in breast milk are approximately 40–50% lower than those of maternal serum and are unlikely to cause harmful side effects [8, 66, 69, 71]. Allergic reactions have been reported in nursing infants in the form of acute watery diarrhea, but this disappears when the drug is discontinued [71, 73, 74]. Olsalazine may pass into breast milk and in animal studies, it has been shown to cause slowed growth and other problems during nursing; caution should be exercised when this drug is administered to a nursing woman.

Electrolytes and Supplements

In a pregnant patient with diarrhea or persistent vomiting, it is an imperative to restore fluid and electrolytes. Furthermore, in a patient with ileostomy, nausea, and vomiting associated with morning sickness may be problematic. Fluid and electrolyte imbalances can occur rapidly under these conditions, causing dehydration.

Folate supplements, 2 mg/day, recommended for all pregnancies to reduce the risk of neural tube defects, are especially important for those taking sulfasalazine because the sulfapyridine moiety in sulfasalazine competitively inhibits the brush border enzyme folate conjugase [40] and therefore inhibits absorption of folate (Table 8.2). Other 5-ASA drugs do not contain sulfapyridine and do not carry the risk of folate malabsorption.

Fish oil supplements are used by some patients with IBD as an adjunct to medical therapy. A randomized controlled trial of fish oil supplementation demonstrated prolongation of pregnancy without detrimental effects on growth of the fetus

or course of labor [75]. Fish oil supplements are not rated by the FDA since they are not classified as a drug.

Corticosteroids (FDA C)

Moderate to severe disease is treated with corticosteroids which are well tolerated and appear to be relatively safe [76–79]. Although the risk of cleft lip and palate, especially with first-trimester exposure is often cited [80], the Committee on Safety of Medicines in the UK concludes that there is no convincing evidence of such congenital abnormalities being associated with corticosteroids in humans. However, the increased risk appeared to be in women taking steroids to treat asthma, not IBD. Corticosteroids vary in their ability to cross the placenta; 88% of *prednisolone* is deactivated to a less active metabolite as it crosses the placenta resulting in low fetal blood concentrations. There is no convincing evidence of teratogenesis in humans [81–83]. If a flare does arise during pregnancy, most patients can be managed successfully with aminosalicylates or corticosteroids, with normal pregnancy and successful delivery [65]. Perinatologists should be cautious when dealing with a newborn whose mothers received high-dose methylprednisolone in late pregnancy because life-threatening adrenal suppression can occur [84]. These newborns could require *hydrocortisone* supplementation and intensive therapy. Rectal preparations may be used until the third trimester unless there is a specific concern about miscarriage or premature delivery. *Budesonide* should be given, whenever possible, in ileocecal CD [40]. Budesonide during pregnancy demonstrated no increase in maternal adverse events when using 6–9 mg/day for 8 months or longer [85].

Corticosteroids are poorly excreted in breast milk (5–25% of the maternal serum concentrations), and the amount received by the infant is minimal. Doses of prednisolone up to 40 mg daily are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses may theoretically have a degree of adrenal suppression, but the benefits of breastfeeding are likely to outweigh the risks. A 4 h delay following oral exposure has been suggested to minimize fetal exposure [86]. Breastfeeding for mothers on steroids appears to be safe.

Thiopurines (FDA D)

Immunosuppressive treatment with severe disease is mandatory during pregnancy due to a higher rate of adverse pregnancy outcomes which are related to disease activity. Although *thiopurines* are rated FDA category D (positive evidence of human fetal risk, but potential benefits may warrant its use) and seem to be safe and well tolerated during pregnancy [63]. Thiopurines are transported by passive transplacental transfer. Smaller studies found an increased risk of congenital malformations, perinatal mortality, and preterm birth [87, 88], while larger studies did not show statistical difference regarding rates of spontaneous abortion, abortion as a result of a birth defect, major congenital malformations, neoplasia, or increased infections after the intake of *6-mercaptopurine* (6-MP; standard dose 1 mg/kg) [89–91]. Some of these conclusions are questioned due to a small number of patients received 6-MP during the entire pregnancy, with a variable dosage of 25–175 mg/day [92]. AZA (standard dose 1.5 mg/kg) crosses the placental barrier, but the fetus does not have the enzyme to convert the drug into its active metabolites, a fact that would explain the lack of adverse effects [93]. In one small study, two of seven patients have taken azathioprine (one patient concurrently took mesalazine). One case ended with abortion (placental abruption) and one case with preterm (37th week) delivery [24]. IBD in all patients in this study was in quiescent phase. The evidence favoring continuing 6-MP/AZA during the pregnancy is based on the following:

1. Studies have concluded that these drugs are safe.
2. Most adverse reactions to 6-MP/AZA occur early, soon after the drug is started. Therefore, the coincidence of any other toxicity to 6-MP in pregnancy most likely must be attributed to active disease.
3. The most virulent factor with toxic complications during pregnancy is active CD, and if the patient is in a remission just achieved by the drug, it should not be stopped.

On the other hand, in a study from Lenox Hill Hospital, there was a 23% incidence of spontaneous abortions (vs. 13% in IBD controls), a 3% incidence of ectopic pregnancies (compared with none in IBD controls), and finally an abnormal amniocentesis in two patients (and none in the IBD controls). There is no conclusion about the risk or the safety of immunosuppressives taken before or during pregnancy, and compromise solution is:

1. Given that the most important issue is active CD at conception, if the patient has already been started on the immunosuppressive drug, it should be continued, and the dose even increased if the clinical severity of the disease warrants it.
2. If the IBD is in remission and has been for months or for years, there is no contraindication to stopping the drug at or before the diagnosis of pregnancy since data has shown that any exacerbation is not likely to occur immediately or for that matter even for months, by which time the pregnancy may be ended or at least the fetus is protected through the first trimester when theoretically it would be most susceptible to any danger. Should an exacerbation occur earlier in the pregnancy, the choice may be made to reintroduce the drug.
3. Decisions whether to continue 6-MP/AZA require rigorous clinical judgment.
4. Definitive conclusion cannot be drawn due to the dosage differences between the patients and studies. This is an area where rules should not be rigid [8, 88, 89, 94, 95].

If the woman has been in remission for a long time, it seems reasonable to stop the drug until delivery since recurrence is very unlikely. If recurrence does develop, then the drug can be restarted at that time. If the patients have active CD or have been in remission only briefly following a severe attack, continuation of the drug is recommended.

The manufacturers do not advise breastfeeding in patients on AZA and 6-MP. Even though there is some clinical experience of mothers who have breastfed on these agents with no apparent adverse effects, breastfeeding is not recommended [96]. Study on a large group treated with these drugs did not show increased number of infections in their breastfed children [97]. An average of 10% of AZA peak plasma concentration levels was excreted within the first 4 h after drug intake with a breast milk concentration less than 0.008 mg/kg/day [98].

Cyclosporine (FDA C)

Administration of *Cyclosporine A* (intravenous: 4 mg/kg/day; oral: 8 mg/kg/day) is controversial. In general population, it has been proven to induce remission in patients with fulminant UC rapidly and effectively in patients who did not respond to 7 days of intravenous steroids [99]. Most cases described the delivery of healthy babies [100–104]. In one of these cases, induction of response was delayed resulting in an unusually long cyclosporine A treatment period of 3 weeks [100]. In another, premature delivery with all of its consequences could be related to deterioration of UC or cyclosporine A therapy [105], as both have been reported in the literature, whereas the role of thioguanine still remains unclear. Both drugs are immunosuppressants and are used in combination with steroids and azathioprine, which infers a risk of serious, even fatal, opportunistic infections. Cyclosporine A is highly potent in inducing remission in patients with UC and, despite being rated as FDA category C, seems to be safe when used at a lower dosage, aiming for blood levels of 200 ng/mL [103]. In general population, patients not responding to these agents within 5–7 days should be considered for colectomy, and responders should be closely monitored for infections [106].

In pregnant patients with severe steroid-refractory UC, cyclosporine or infliximab is the main medical options. Intravenous cyclosporine has a shorter time to clinical response but is FDA category C, and breastfeeding is not recommended because of immune suppression, neutropenia, adverse effects on growth, and carcinogenesis [96, 107]. Dynamics of cyclosporine excretion into breast milk is reported (Fig. 8.2), but neonatal serum levels are mostly

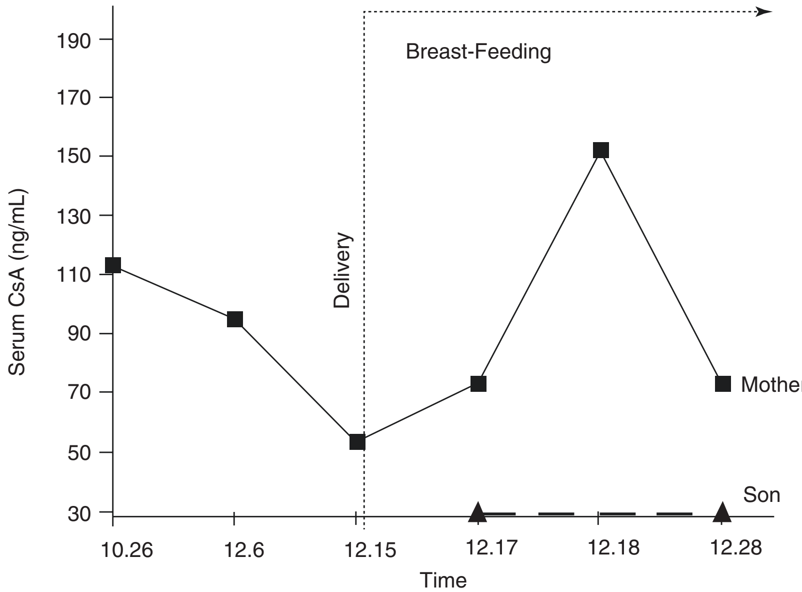

Fig. 8.2 Maternal and infant serum cyclosporine levels prior to delivery and 2 weeks into puerperium (units: ng/mL, normal therapeutic range: 100–400 ng/mL). Reproduced with permission from [104]

low or undetectable without consequences to the baby [108].

Immunomodulators (FDA B)

In pregnant patients with severe steroid-refractory CD, cyclosporine or infliximab is the main medical options. *Infliximab* (IFX) has a longer time for response than cyclosporine in severe CD. It is believed that the chimeric structure of the IFX molecule containing a human IgG_1 constant region limits placental transfer during the first trimester [109]. Preferential placental transport occurs for IgG_1, followed by IgG_4, IgG_3, and finally IgG_2 [110]. Immunoglobulin transport occurs in a logarithmic fashion as the pregnancy progresses, with the majority occurring in the third trimester. Therefore, discontinuation of biologics early in the third trimester is posted to decrease the exposure to the fetus because preferential IgG transport is highest during this time [111]. Placental transfer of IFX was first published as a case report in 2006 [112]. As other maternal antibodies, IFX has a prolonged half-life in the newborn [111, 112]; there are persistent therapeutic IFX levels in infant cord blood several weeks after cessation of therapy [107, 113]. Maternal transfer of IFX has been reported when doses of 10 mg/kg throughout pregnancy were used. The drug was seen to persist in the baby for 6 months, but it is not known whether this induces antibody formation although this would seem unlikely. Placental transfer of IFX) was not seen when doses of 5 mg/kg up until week 30' gestation were used [114]. Long-term implications of IFX exposure during early childhood development are unknown. These findings suggest that pregnant patients should avoid therapeutic antibody treatments after 30 weeks of gestation, and if necessary, the expectant mother can be bridged with steroids to control the disease activity until delivery [112, 115]. The transfer of anti-TNF antibodies to the fetus during the last part of pregnancy may mean exposure of the neonate in the first months after birth, raising potential concerns about infection and response to vaccines [116]. Non-live vaccines can safely be given to immunocompromised individuals (including neonates exposed to anti-TNF drugs) and mostly lead to an adequate humoral immune response [117]. The birth outcomes of women treated with IFX were comparable with those of the general population or of pregnant women with CD who were not treated with IFX [118, 119]. Postmarketing data from Centocor of more than 280 pregnancies, of which a third had IFX during the first trimester, showed that 75% had live births, 14% had a miscarriage, and 11% had therapeutic terminations [120]. The benefits of

achieving and maintaining clinical remission in patients receiving IFX) during pregnancy superseded the potential risk of exposing the unborn child to the medication [111]. The 2% receiving infliximab at the time of conception discontinued therapy during pregnancy [30].

> The US FDA and the European Crohn's and Colitis Organization (ECCO) categorize anti-TNF agents as safe during pregnancy.

A pregnant woman with treatment-refractory CD who failed treatment with IFX) can successfully be treated with *adalimumab*, a recombinant human IgG_1 monoclonal anti-TNF antibody [121]. A recent study has shown that infants born to mothers who have received adalimumab up to 56 days before delivery have therapeutic levels of adalimumab in cord blood and in serum up to 7 weeks after birth [122]. A limited number of case reports in which adalimumab use during pregnancy is followed by the birth of a healthy child has been published to date [116, 122, 123]. Although clinical data are scarce up to now, adalimumab is also considered low risk during preconception and in at least the first two trimesters of pregnancy [116]. Another case reported the use of *etanercept*, a soluble TNF receptor fusion protein that binds to and inactivates TNF, in an uneventful pregnancy of a patient with refractory rheumatoid arthritis [124]. Etanercept has been shown to be excreted in breast milk, but it is not known whether the drug can be absorbed orally because it is such a large protein [125]. *Certolizumab pegol* is Fab' fragment that is not actively transported across the placenta as are other IgG molecules. However, other mechanisms exist by which agents are transported across the placenta. Other commercially available Fab' fragments have been detected in newborns, and further study is needed to delineate the pharmacokinetics of certolizumab pegol in pregnancy. There is no reason to believe that this agent will affect pregnancy outcomes differently from the other TNF antagonists. *Natalizumab* is pregnancy category C. It is an IgG_4 to α-integrins and therefore has a different mechanism of action from the other biologics; it also has a different architecture. Pregnancies reported during clinical trials in CD have not led to any signals regarding adverse events, but the total number of patients exposed is small.

IFX has not been detected in human breast milk of nursing mothers [111, 112, 114, 126]. Also, IFX)was present in the mothers' sera but not in the infants' sera [114]. Physicians should be aware that the fetus may be exposed to therapeutic monoclonal antibodies when administered to pregnant patients, and the long-term implications on the child's developing immune system are unknown at this time. No information is currently available regarding adalimumab transmission in breast milk.

Methotrexate (FDA X)

Methotrexate (MTX) is teratogenic and toxic and is contraindicated in pregnancy and breastfeeding. If conception should accidentally occur, therapeutic abortion should be discussed, although not mandatory. MTX should be stopped immediately and high-dose folic acid replacement started. The intracellular metabolites of MTX, methotrexate polyglutamates, have a long half-life and take about 6 weeks to reach steady state or to completely wash out. Thus, women who wish to become pregnant should stop MTX for 3–6 months.

Thalidomide (FDA X)

Thalidomide and its analog *lenalidomide* partly counteract the effects of TNF-α and have been used in the treatment of refractory CD in general population, although currently available systematic evidence does not clearly demonstrate the benefit of these drugs [127, 128]. Thalidomide has extensive teratogenic sequel including limb defects, central nervous system effects, and abnormalities of the respiratory, cardiovascular, gastrointestinal, and genitourinary systems. Thalidomide is contraindicated during pregnancy and breastfeeding. Women of childbearing age taking thalidomide should use two methods of contraception 1 month prior to starting therapy, during therapy, and for 1 month after stopping therapy [127, 128]. If conception should accidentally occur, therapeutic abortion should be discussed, although not mandatory. Although

lenalidomide appears less teratogenic in animal studies, exhibiting only teratogenic properties in rabbits at doses with maternal toxicity [63], its structural analogy with thalidomide and the lack of studies demonstrating its safety are absolute contraindications for using this drug in pregnant patients or patients wishing to become pregnant.

Probiotics

Probiotics that are approved in the management of IBD do not appear to cause any safety concerns for pregnant women [129, 130]. Systemic absorption is rare when probiotics are used, and the data do not indicate any increase in adverse pregnancy outcomes [131].

Enteral/Parenteral Nutrition

There have been a few reports from the 1980s documenting the necessity of treating particularly severe relapses of CD during pregnancy with total parenteral nutrition [132–134]. Although successful, total parenteral nutrition is often associated with significant morbidity including sepsis, catheter thrombosis, etc. Enteral treatment with elemental diets seems to be a safe alternative to total parenteral nutrition in pregnancy [135]. Remission rates with an elemental diet in uncomplicated CD are reported at 85%, which compare favorably with steroids and total parenteral nutrition in general population [136, 137]. Effects of elemental diets are presented in Fig. 8.3.

Total parenteral nutrition has been used in pregnancy for short periods for the management of hyperemesis gravidarum and severe eclampsia and to maintain fetoplacental function just before delivery. It has rarely been required for longer periods to sustain a pregnancy. Heller back in 1977 recommended avoidance of fat emulsion in pregnancy because of the theoretical dangers of maternal ketonemia, premature labor, and placental infarction due to fat emboli.

Antidiarrheal Agents

The routine use of this antidiarrheal is not recommended in nursing mothers: diphenoxylate hydrochloride-atropine sulfate is excreted in breast milk, and atropine may inhibit lactation.

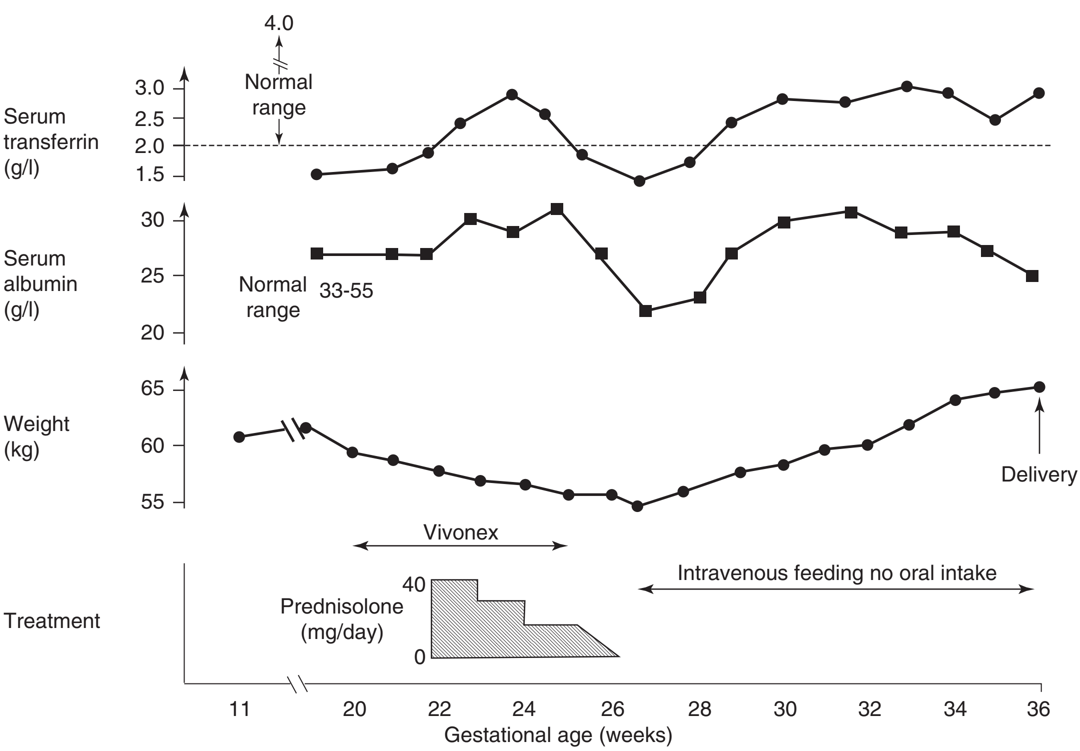

Fig. 8.3 Progress and treatment during pregnancy complicated with Crohn's disease without and with intravenous feeding. Reproduced with permission from [134]

Loperamide is transferred into breast milk but is unlikely to affect the child [82].

8.1.7.2 Surgical Treatment

Active CD can be controlled with medical therapy during pregnancy in the majority of cases. Only about 2% of the patients require surgery [138]. Decisions to operate on a pregnant woman with CD should be guided by the principle that if a surgical intervention is the best for the mother, it is usually also the best for the unborn child.

> Indications for surgery in pregnant women with CD are the same as for nonpregnant patients and include perforation, obstruction, major bleeding, and abscess.

Elective Surgery

Intra-abdominal surgery performed during the first trimester is associated with an increased risk of miscarriage; for planned procedures in the second trimester, the risk is lower. In the third trimester, a laparotomy may be complicated by premature delivery and technical difficulties (see Chap. 23). However, the severity of the CD, not the operation, determines maternal and fetal risk (see Sect. 8.1.8.3).

Emergency Surgery

When a woman with a history of CD presents with peritonism, the possibility of an acute manifestation of the disease must be considered. In such circumstances, surgery should not be delayed significantly.

Colorectal Crohn's Disease

> - Surgery could be delayed where aggressive medical therapy may allow critical fetal maturation
> - With bowel perforation and diffuse peritonitis, removal of the source of sepsis and exteriorization of the bowel ends is indicated [139]

Active intraperitoneal sepsis increases the risk of anastomotic leakage and miscarriage. Intestinal stomas seldom cause difficulty. If, after delivery, the residual bowel is healthy, reanastomosis can be performed. A stomal therapist should mark the patient before surgery. In pregnant patients, the optimal location for the stoma on the abdominal wall is usually higher than normal because the stoma will drop to a lower position after delivery.

After colectomy, a decision should be made regarding the rectal stump. Stump breakdown and leakage leading to intra-abdominal sepsis is a major concern. The stump can be handsewn in two layers and wrapped with the omentum or brought out as a mucus fistula. If a mucus fistula is to be placed, the remnant stump should be kept long. Because of the enlarged uterus, the stump will need to be brought out through an extraperitoneal plane deep to the broad ligament and dilated ovarian vessels. The rectum is irrigated with Betadine at the time of surgery to remove the excess bloody mucoid material and a rectal tube left in place to keep it decompressed in the postoperative period [140].

It is not known when the medical therapy should be continued after IBD surgery during pregnancy and whether this possible interval without medical therapy influences disease activity during the continuation of pregnancy.

Small Bowel Crohn's Disease

The indications for small bowel surgery in pregnant women with CD are not different from the general population and include intestinal obstruction or perforation, hemorrhage, or abscess. A temporary ileostomy is generally preferred to reduce the risk of postoperative complications that can be seen after primary anastomosis. Budesonide should be given, whenever possible, in ileocecal CD [40].

Presentation Mimicking Acute Appendicitis

Several questions arise here. First is the question of abdominal wall incision. If acute appendicitis is questionable preoperatively, it is better to perform laparoscopic exploration. If an indication for bowel resection exists (abscess adjacent to active ileocecal disease, bowel

perforation, bowel obstruction), median laparotomy is preferable. Another question is when active ileocecal CD is present without perforation, obstruction, or adjacent abscess, should a surgeon do the bowel resection [141]. Logically, when the abdomen is already open and active disease is found, it is better to resect it, to prevent exacerbation during ongoing pregnancy. The severity of the CD is the main cause of the poor fetal outcome.

8.1.7.3 Anesthetic and Perioperative Management

See Chap. 21.

8.1.7.4 Obstetric Management

Prevention and Treatment of Preterm Labor

See Chap. 23.

Mode of Delivery

In 1972 authors stated that in the case of an unplanned pregnancy occurring in a patient with active CD whose family is already complete, there are strong indications for suction termination in the first trimester [142].

> Pregnancy termination should never be considered as a therapeutic option for CD flare-up as there is no evidence to suggest that induced abortion improves disease activity.

The best mode of delivery still remains controversial as no randomized prospective studies have been published. Crohn et al. in 1956 considered that the percentage of CS does not increase [17]. The *Royal College of Obstetricians and Gynaecologists* and the *American College of Obstetricians and Gynecologists* do not have special guidelines with regard to pregnancy and CD. There is an increased rate of CS in women with IBD [143]. Using the *2005 Nationwide Inpatient Sample*, with 2372 CD deliveries and 1368 UC deliveries, the adjusted odds of a CS were higher in women with CD (aOR 1.72) and UC (aOR 1.29) compared to non-IBD controls [144]. One meta-analysis claims that CS rate is higher only in CD patients and not in UC patients [145]. No data exist on whether the CS were elective or emergent and whether the outcomes of the infants differed after vaginal delivery and CS. In one national Dutch study, overall CS rate of 32% in women with CD was present [25] which is substantially higher than 13.6% incidence of CS in the Netherlands [146]. Some studies reported that the risk of incontinence and anal sphincter tears is less in CS than in vaginal delivery [147–150]. This is disputed in other studies, which say that anal sphincter tears that occur in vaginal deliveries do not affect continence [151] and that vaginal delivery reduces surgical procedures and adhesion formation in a group of high-risk patients.

Disease progression within 2 years after childbirth was significantly more frequent in those patients with the active luminal disease compared to women with inactive luminal disease prior to pregnancy, and this was independent of the mode of delivery [25]. This suggests that CS does not prevent worsening of CD (over a median follow-up of over 4 years) [152].

> The mode of delivery does not influence the natural history of IBD. Vaginal delivery is not associated with increased risk of subsequent perianal disease in women with CD.

Elective Cesarean Section

In general, the indications for elective CS are (ECCO guidelines) [153]:

> - Obstetric
> - *Active* perianal disease (abscess and/or fistula)
> - Rectal involvement

Obstetric indications for CS are out of the scope of this book.

A perianal fistula or an abscess was considered to represent perianal CD; however, anal fissures or hemorrhoids were not [154]. The preexistent perianal disease is present in nearly 25% of patients [25]. Patients with inactive perianal disease or no history of the perianal disease are not at increased risk for perianal disease after a vaginal delivery [27, 154, 155]. The progression of perianal disease was observed significantly less frequently after vaginal delivery than after CS, with the same trend in patients with and without perianal disease prior to pregnancy [25, 27]. These results should be taken with caution because indications for CS could be confounding factor. The prior perianal disease may increase the risk for allocation to a CS and also the risk for perianal disease progression by itself.

Another issue in patients with CD who will undergo vaginal delivery is the question if episiotomy may influence perianal disease. There is a perception that vaginal delivery and episiotomy in CD patients with the active perianal disease would be complicated by disease extension, rectovaginal fistulas, and non-healing perineal wounds [156]. Brandt et al. reported that patients with CD without preexistent perineal involvement, who delivered vaginally, usually with episiotomy, had 18% chance of developing perianal involvement [156]. Fortunately, newer and larger studies cannot support these findings [25, 154]. Women with the active perianal disease all reported worsening of perianal symptoms postpartum, while those with inactive disease remained quiescent over a 2-year follow-up [154]. The results from Ilnyckyji et al. are interesting because episiotomy was performed in an equal percentage of patients with active and inactive perianal disease. The group with the inactive perianal disease had a higher percentage of second- and third-degree lacerations. It is obvious that patients with histories of the previous perianal disease may receive more vigilant attention to their perineum during delivery. There are several unknown facts from the data in this study. One is *Perianal Disease Activity Index*, important for comparison of the results and also the activity of the disease in general because the subclinical infection can be present which can only be confirmed by colonoscopy and/or biopsy. Also, there are several types of episiotomies (not mentioned), and the length is not mentioned and compared [154].

Emergent Cesarean Section

In patients presenting with acute abdomen, the treatment depends on the trimester of pregnancy. During the first two trimesters, only surgical treatment of the cause of acute abdomen is carried out. After surgery without CS, fetal monitoring should begin in the postanesthesia recovery room, and the patient should be watched carefully for spontaneous labor. After 28 weeks of pregnancy, CS during operation for acute CD is recommended due to a higher incidence of postoperative complications leading to spontaneous induction of labor [140, 157].

8.1.8 Prognosis

8.1.8.1 Maternal Outcome

Maternal Morbidity and Mortality

The *Nationwide Inpatient Sample,* used to study pregnant IBD patients and outcomes for mother and infant (more than 5000 pregnancies in IBD), found higher rates of maternal venothrombotic complications and malnutrition [144]. Poor maternal weight gain during pregnancy in CD patients with quiescent disease at conception is present [158].

The patients with ileostomies have been shown to be capable of normal pregnancies [79, 156, 159]. Patients with ileostomies were shown to have lower hemoglobin during pregnancy [160] but apparently without ill effect. Stomal problems of displacement and prolapse are not uncommon but remit postpartum. Vomiting has been reported to cause stomal prolapse requiring revision after delivery.

Back in 1972, there was a concern about patients with abscess and fistula formation, because, in the puerperium, the rapid involution of the uterus may tear apart adhesions which wall-off abscess cavities, thus leading to spreading peritonitis [142]. During the 1960s, the mortality rate was about double that expected in the general population [77, 161]. Five of the six patients described in the series by Hill et al. had a

free perforation of CD. The maternal mortality was nil [139]. Further studies did not find higher maternal mortality than in general population. It might, therefore, be assumed that conception took place more readily in these patients whose disorder was less florid.

Fertility and Sexual Health

The effect of CD on fertility is controversial. Some studies, especially older, claimed that fertility is subnormal [77, 159], starting in 1956 with Crohn (et al.) itself [17]. Relationships, sexual health, and fertility in IBD patients are interrelated. Chronic IBD decreases the quality of life [162]. The symptoms of IBD, including diarrhea, problems with continence, and weight loss undoubtedly, have an effect on body image particularly in adolescents and young adults. Older studies, as in Crohn et al. [17], found that vitamin B_{12} deficiency occurred in about 60% of patients, as is to be expected in any group of such patients who had undergone intestinal resection. Some of these patients became pregnant within 6 months of starting vitamin B_{12} therapy.

The side effects of treatment such as weight gain due to steroids may also cause feelings of unattractiveness and loss of self-esteem. Children with IBD may experience delays in growth and puberty, and this also has a serious effect on confidence and body image. Young people with IBD may, therefore, experience difficulty in forming intimate relationships and worry that they may not be able to have a normal sex life. Fear of inheritance of IBD in the offspring and fear of fetal exposure to IBD therapies can lead to voluntary childlessness. Stoma surgery is a major life event, particularly in teenagers [163]. The development of IBD may put great strain on a previously good relationship, and women who are in a relationship experience more difficulties in their sexual life than nonaffected women of a similar age [164, 165].

Variables such as systemic effects of the disease, for example, fatigue and anemia, as well as medication effects, such as corticosteroids, on libido can impact sexual activity. Postoperative dyspareunia can similarly affect sexual activity and impact the chance of conceiving [77]. Dyspareunia, the involvement of the Fallopian tubes in the disease process, general ill health, and medical advice against pregnancy have all been implicated [8, 166]. Dyspareunia and vaginal candidiasis are more common than in healthy women, which may account for some of these difficulties [167]. Many women experience some change in their menstrual cycle in the year preceding IBD diagnosis. Changes in cycle length were most common, followed by changes in the duration of flow and changes in menstrual pain [168–171]. Although the potential causes of menstrual irregularity are vast, it has been suggested that the menstrual cycle is used as an additional vital sign in the assessment of well-being and the exclusion of pathologic conditions [172]. Thus, eliciting if a woman with suspected IBD has experienced changes in her menstrual cycle may provide the clinician insight into the nature and severity of the underlying disease. Among women with baseline dysmenorrhea who experienced a change, the majority reported their menstrual pain to be more intense and of longer duration in the year before IBD diagnosis. This finding may be because of pathophysiologic mechanisms that are common to IBD and primary dysmenorrhea. Some authors have speculated that prostaglandins when released from sloughing endometrium during menstruation induce uterine contractions and menstrual pain [173] and may also play an important role in the abdominal pain and diarrhea experienced by patients with IBD due to increased contractility of gastrointestinal smooth muscle [174]. Alternatively, this finding may be due to the misperception of IBD symptoms as worsening menstrual pain. Given the overlap in symptoms between active IBD and dysmenorrhea (e.g., nausea and vomiting, loss of appetite, diarrhea, general aching, irritability, sleep disturbances, and depression), symptom confusion may certainly occur.

As the local balance between fibrinolysis and clotting processes in the endometrium controls the volume and duration of menstrual bleeding and hypothalamic/pituitary hormones control menstrual cycle length, it was postulated that IBD likely does not affect the local endometrial environment or hormone release [168]. If endometrial thickness, an important determinant of fertility and in vitro fertilization success, and hypothalamic/pituitary hormone release are truly unaltered in

IBD, this would correlate with the normal fertility rates reported in the literature for women with IBD who have not undergone surgery [175, 176]. It would also suggest that women with IBD undergoing in vitro fertilization are not at decreased odds for endometrial implantation or in vitro fertilization success. Cycle regularity changes significantly over time wherein more regular cycles were found for each year of greater disease duration. For young women desiring natural pregnancy, this is an important finding because it can reassure them that over time their cycles should become more predictable. Although IBD treatment and disease control may play a role, cycle regularity improved regardless of disease activity and after controlling for changes in BMI. Steroid use is associated with more irregular cycles even after adjusting with propensity scores [168].

Fertility appears to revert to normal after induction of remission in women with CD. Women who have their first pregnancy after the onset of IBD have fewer pregnancies than population controls, whereas women who became pregnant prior to the onset of IBD have a similar reproductive history [175]. In addition, women with CD have a delayed age of first pregnancy after being diagnosed [177] and have been shown to have fewer children than might be expected after diagnosis with a higher rate of failure to conceive [166]. These are probably some of the reasons for the lower incidence of IBD in pregnancy.

Surgery for CD may decrease fertility compared with medical therapy alone. Development of postoperative pelvic adhesions contributes to higher infertility rate [176]. On the contrary, others claim that patients who have undergone resections have been said to have higher pregnancy rates due to the elimination of active disease itself and subsequent nutritional deficiencies [159]. If the disease is not active, sexual desire rises. CD patients had a higher rate of birth control, were having sexual relations, and were advised by their physicians not to become pregnant. Patients with CD had a notable reduction in the number of children born and a substantial increase in the incidence of prematurity. The rate of miscarriage and CS was unaffected by CD. The site of the disease did not affect these findings.

In a conclusion, in adequately treated and nourished pregnant CD patients, and in community-based and population-based studies, women with IBD have similar infertility rates compared with the general population (5–14%) [19, 175, 176]. Subfertility is mainly reported in CD patients with active disease [42, 166].

8.1.8.2 Fetal Outcome

Inheritance of CD

Patients are naturally concerned about passing their disease on to their offspring. Unfortunately, family history is the strongest predictor for developing IBD. If one parent is affected, the risks of the offspring developing IBD are 2–13 times higher than in the general population [178–180]. One study estimated that the risks of IBD in first-degree relatives of probands with UC and CD were 1.6% and 5.2–7.5%, respectively, and even higher values in the Jewish population [29, 180, 181]. If both parents have IBD, the risk of their offspring developing IBD over their lifetime was estimated to be 35% [180, 182].

Several studies suggest that breastfeeding may be protective against the development of IBD in the infant. In a meta-analysis of 17 studies, the 8 highest quality studies showed a pooled odds ratio of 0.45 (0.26–0.79) for CD and 0.56 (0.38–0.81) for UC [183]. However, these were not mothers who had IBD themselves.

Perinatal Outcome

Pregnancy outcomes depend on the disease activity at conception or during pregnancy. Patients whose CD is in remission at the time of conception have pregnancy outcomes similar to those in the general population [26, 184]. Active disease at conception is associated with a higher rate of fetal loss, preterm birth (twofold), LBW (threefold), and small for gestational age infants [24, 33, 36, 37, 78, 143, 145, 185–188]. Preterm delivery is further associated with disease flares during pregnancy [33, 189]. One hypothesis is that an increase in circulating prostaglandin levels during a flare could initiate preterm labor with the induction of smooth muscle contraction [190, 191]. Another theory is that the role of increased

gut permeability during increased inflammation could alter nutritional and immunological factors affecting labor [190]. Other potential predictors of an adverse outcome include ileal CD [158] and previous bowel resection [158, 184]. In the general population, smoking is a known risk factor for LBW infants and for disease activity in CD women [9]. Pregnant CD patients who smoke are at a substantially increased risk for LBW and preterm delivery [9, 192]. Analysis of studies after the year 2000 showed no increase in the incidence of small for gestational age [145].

Subclinical infection is another problem. Although the women are free of symptoms at the beginning of the pregnancy, it is possible that inflammation may have been present on colonoscopy and/or biopsy and that this subclinical inflammation is responsible for the higher rate of small for gestational age births [158]. These women felt too well to present for investigation, and so such data are unavailable.

Infection and inflammation, in general, have been correlated with an increased risk of pregnancy complications such as preterm birth and premature rupture of membranes (see Chap. 23). Possible candidate genes in the cause of preterm birth include the TNF-α, TNF-receptor 1, and TNF-receptor 2 alleles [193], suggesting another possible link with IBD. A meta-analysis including more than 700 patients with CD reported a normal pregnancy in 83% (71–93% in individual studies). Fetal malformations were observed in 1% of all pregnancies, and the frequency of spontaneous abortions and stillbirths was similar to that observed in the general population [194].

Predictors of poor outcome (preterm birth, LBW, intrauterine growth retardation, small for gestational age infants, congenital anomalies, Apgar scores, stillbirth, and complications of labor) are having active IBD, either UC or CD, previous surgery for IBD, and nonwhite ethnicity [57, 184]. The most common area of resection is the terminal ileum, and the loss of the terminal ileum's capacity for nutrient and vitamin absorption could predispose to smaller birth weight. Secondly, the fact that resection had previously occurred may serve as a marker of greater disease severity. In one small prospective study, there were no significant differences among pregnant women with IBD and nonpregnant women with IBD as far as the percentage of patients with previous surgery was concerned [24]. There is a correlation between the length of bowel resection or active disease at the time of conception and an increased risk of spontaneous abortion as compared to a reference population and to women with UC [32].

Crohn et al. in 1956 considered that the percentage of stillbirths, miscarriages, or spontaneous abortions does not increase [17]. Primiparous CD patients have a higher decrease in birth weight in comparison with multiparous CD patients after adjustment for confounding factors [36]. Abnormal birth weight, stillbirth, spontaneous abortion, and congenital abnormalities (contrary to the patients with UC) are no more common (in inactive disease during pregnancy) than in the population without IBD [19]. Also, the disease activity was not predictive of an adverse outcome in any category [184] but in active disease, there is an increased risk for stillbirth [33]. Three retrospective studies have, however, shown higher incidences of LBW and preterm birth but made no correlation to disease activity [36, 143, 186]. The majority of patients in this cohort with both UC and CD, however, did have inactive or mild disease throughout pregnancy. Similarly, a population-based study from Denmark also did not find an increased risk of adverse events associated with disease activity [195]. They reported that women with active disease had mean adjusted risks of LBW, LBW at term, preterm birth, and congenital anomalies of 0.2, 0.4, 2.4, and 0.8, respectively. However, the crude risk of preterm birth was increased, with an odds ratio of 3.4 in those with moderate to high disease activity. Overall, these two population-based studies did not show a significant role of disease activity in predicting adverse outcomes above that expected with the diagnosis of IBD alone. The abortion rate in patients with CD in the 1960s was 13–15% [17]. Turnbull's group in 1970 found the difference in the distribution of the CD lesions which may be a significant factor for different perinatal outcomes. Large bowel CD has worse perinatal outcome compared to ileal CD [196]. In view of the potential for adverse pregnancy outcomes in

IBD, such women should be referred routinely as cases of high risk, regardless of disease activity. Recently, a small case series from Manchester recently reported six women who had surgery for intraperitoneal sepsis in CD during pregnancy. Five healthy babies resulted from these pregnancies although one miscarriage occurred in a patient with a surgical complication [139].

Prevention of preterm labor and birth is described in detail in Chap. 23.

Breastfeeding

Although the *American Academy of Pediatrics* recommends breastfeeding for at least 6 months after birth [197], many women who require drug therapy initiate breastfeeding less frequently, discontinue breastfeeding earlier than women who are not receiving medication [198], or do not breastfeed at all [35]. First, breastfeeding protects against many immune-mediated diseases such as bronchial asthma, atopic dermatitis, allergic rhinitis, and type I diabetes mellitus. This effect is attributed to the immunomodulatory properties of human milk. It is known that heredity has its role in in the development of IBD; however, environmental factors (such as smoking status) are also important [199, 200]. Some data suggest that breastfed infants may be at decreased risk [181], and others claim statistically significant protective role against UC and an even greater role against CD [183]. Therefore it should be insisted on breastfeeding minimally for 6 months and up to 2 years if possible. Unfortunately, most studies did not define duration and exclusivity of breastfeeding precisely, and it was not clear whether exclusive breastfeeding was being compared with nonexclusive breastfeeding or whether nonexclusive breastfeeding was being compared with exclusive bottle-feeding. Thus, it cannot be stated whether the absence of breastfeeding is the risk factor for IBD or the presence of bottle-feeding [183].

Pregnancy Outcomes After Emergency Surgery

Emergency surgery during pregnancy has been reported to be associated with a high risk of fetal loss (60%). Five of the six patients described in the series by Hill et al. had a free perforation of CD, and one fetus was lost [139]. Multiple case reports of small bowel surgery for CD during pregnancy historically had revealed high mortality to both the mother and the fetus; however, more current reports reveal better outcome [201]. A case series of six surgeries from 11 to 30 weeks gestation for intraperitoneal sepsis from CD reported successful deliveries of healthy infants at or near term (one delivered at 31 weeks) in five cases and one patient had a miscarriage [139].

8.2 Ulcerative Colitis

8.2.1 Incidence

UC was first described by the)British physician Sir Samuels Wilks in 1859 [202]. An association between UC and pregnancy was noted by Gossage and Price at a symposium held at the *Royal Society of Medicine* in 1909 [203]. UC preferentially affects women between the ages of 20 and 39 years and does not impair fertility. Estimation from 1956 was that up to 50% of females who develop the disease before the age of 45 will subsequently become pregnant [204]. The first description of two cases of toxic megacolon as a consequence of UC was described by Holzbach in 1969 [205]. Up to 7% of patients will present the first colitis episode during pregnancy or puerperal period [83].

Although UC and pregnancy frequently coexist, therefore, it is rare for fulminating disease to ensue and require an operation to save the mother's life before or after delivery. Up to 1987, there were only 35 cases in the literature [20, 79, 205–213]. It is even rarer to have patients operated for UC before pregnancy presenting as acute abdomen during pregnancy. The causes of small bowel obstruction in operated patients are small bowel adhesions, small bowel volvulus or external compression of gravid uterus on IPAA, or small bowel proximal to IPAA [214, 215].

8.2.2 Effect of Pregnancy

Disease in general population can be basically classified into mild, moderate, and severe for

management and prognostic purposes according to *Truelove criteria* based on bowel movements per day, fever, heart rate, anemia, and sedimentation rate [216]. Specific classification of pregnant patients, with UC, as well as CD, is in four categories:

- Inactive at conception
- Active at conception
- Arising during gestation
- Arising during the puerperium

It has been reported that 30–50% of female patients with UC will have an exacerbation while pregnant or in the early postpartum period [217]. Willoughby and Truelove found that patients with UC who had the inactive disease at conception tended to remain so during the pregnancy, whereas those with active disease had continued and even worse disease activity [83]. Others show that around 50% of active cases had improvement and in all cases, it was by the end of the 8th week of pregnancy [79]. Nielsen et al. reported an exacerbation rate of 34% per year during pregnancy and 32% per year when not pregnant in women with UC [78]. If relapse does occur, this is most likely to happen in the first trimester, but the risk to the mother is negligible, provided that the UC is treated vigorously [29, 78, 176, 218].

In general, women with IBD are as likely to flare during pregnancy as they are when not pregnant. Studies from the 1980s reported that 30% of women with inactive colitis at the time of conception will develop an exacerbation of their disease during pregnancy or the puerperium [83, 219, 220], a figure close to the expected recurrence rate in a comparable group of nonpregnant women [78, 221]. Similar findings are confirmed recently [218]. During that decades, up to two-thirds of patients remain symptomatic or deteriorate thereafter when colitis was active at the time of conception [83].

The effects of multiple pregnancies on UC do not show a definite pattern, and although the numbers are small, there is an agreement that there are no consistent effects in successive pregnancies [79].

Relapses of UC usually occur in the first trimester or the puerperium [22, 83, 219, 220, 222, 223]. It has been suggested that the high circulating levels of serum 17-hydroxycorticosteroids during the second and third trimesters induce remission at this time [221]; levels fall sharply following delivery. Although cortisol comprises 90% of total plasma 17-hydroxycorticosteroids in the third trimester of pregnancy, the increase is actually due to elevated levels of the glucocorticoid-binding protein, transcortin. Biologically active cortisol remains unchanged [220], and there is no increased steroid action in pregnancy. A small prospective study reported a decrease in relapse rate in UC patients 4 years after pregnancy, in comparison with the 3 years before pregnancy [41]. The rates of relapse decreased in the years following pregnancy in comparison to prepregnancy (0.34 vs. 0.18 flares/year) [42]. Severe colitis during pregnancy is rare [224]. It is interesting that one study from Greece found a higher incidence of smokers among pregnant IBD patients in quiescent phase (43%) than normal pregnant women (14%), but due to a small number of patients, the difference was not significant [24].

The only prospective study reported on disease activity in a group of pregnant women with UC compared with nonpregnant women with UC [30]. About 84% were undergoing therapy at the time of conception, and 86% received treatment during pregnancy. The majority used mesalamine, administered either orally or topically, with only 5% on azathioprine; one patient was on cyclosporine at the time of conception, which was then discontinued. Only 65% that were in remission at the time of conception remained in remission, compared with 82% of the nonpregnant control (p<0.0001). HR of 2.74 was found for a disease flare during pregnancy. Women were more likely to experience a flare in the first and second trimesters, and in the first 3 months following delivery, than during the third trimester. Interestingly, if a woman had active disease during the first trimester, her risk of continued activity was no higher than matched controls.

In conclusion, there is a higher risk of disease activity in UC than in CD. It is unclear why UC

Table 8.3 Definition of ulcerative colitis phenotype according to the Montreal classification

Maximal extent of inflammation observed at colonoscopy	
Proctitis	E1
Left-sided e extending up to splenic flexure	E2
More extensive disease	E3

might be so unstable during pregnancy, but one theory is that the shift in the immune environment from one rich in TH_1 cells to one dominated by TH_2 cells promotes disease activity. This shift is caused by a maternal response to the fetus, as a bias toward a TH_2 state is protective of a pregnancy [225].

8.2.3 Classification

All new patients should have their disease phenotype classified in accordance with the *revised Montreal classification* (Table 8.3). Classification attempts to more accurately characterize the clinical patterns of UC [45, 46]. In addition, it could serve for better understanding of the disease dynamics during pregnancy, treatment options comparison, and finally prognosis.

8.2.4 Pathophysiology

8.2.4.1 Free Intestinal Perforation

AS in CD, there are several mechanisms. First, these include perforations due to the primary disease itself; second, perforations after earlier surgical procedures; and the third, during the labor. This third mechanism is especially important because it includes several interrelated mechanisms. If the CS is indicated in a patient after previous surgery for UC, then intestinal adhesions can obstruct the location for uterotomy. Therefore adhesiolysis can be mandatory and can result in the opening of the bowel wall. Another possible mechanism that damage to the bowel serosa can result in delayed intestinal perforation. The third pathophysiology can result after the avulsion of the ileal wall by the rapid retraction of the uterus in the postpartum period both after CS (especially after the previous operation for UC) [226] and vaginal delivery.

8.2.4.2 Toxic Megacolon

This condition is characterized pathologically by severe, transmural inflammation with infiltration of the colonic wall by neutrophils, lymphocytes, histiocytes, and plasma cells. Toxic megacolon is a result of a severe inflammation extending through the smooth muscle layer, possibly causing paralysis of colonic smooth muscle resulting in marked dilatation. There is a correlation between depth of invasion and the degree of colonic dilatation. Neutrophils invade the muscle layer and release proteolytic enzymes, cytokines, and leukotrienes. Nitric oxide, an inhibitor of smooth muscle tone, is released from neutrophils and leads to colonic dilatation. Inflammation and upregulated nitric oxide synthetase are also thought to increase local nitric oxide, which inhibits colonic smooth muscle and causes dilatation [227, 228]. Myenteric plexus involvement is not consistent and probably does not contribute to bowel distention.

Additional factors could also play a role in colonic dilation. Some are specifically associated with pregnancy: (1) tocolysis with ritodrine [205, 229], (2) mechanical obstruction due to an overdistended uterus and bed rest [229], and (3) progesterone-induced smooth muscle relaxation. General factors, not specific to pregnancy, that can precipitate toxic megacolon are (1) anticholinergics, (2) narcotics, (3) hypokalemia, and (4) barium enema.

Anemia is common during pregnancy associated with IBD, and regular surveillance to exclude this may be advisable [160].

8.2.5 Clinical Presentation

8.2.5.1 Elective Presentation

If there is a history of prepregnancy UC, then symptoms suggestive of UC can confirm the diagnosis and speed up the diagnostic workup. If UC presents for the first time and during pregnancy, the diagnosis is more difficult. Symptoms and signs suggestive of UC are the same as in nonpregnant population: tenesmus and increased frequency of stools with the passage of blood and mucus.

Symptoms and signs of extraintestinal manifestations (found in both UC and CD) should be sought: musculoskeletal (arthritis, spondylitis, and sacroiliitis), dermatologic (erythema nodosum, pyoderma gangrenosum, psoriasis, oral aphthous stomatitis, and Sweet syndrome), hepatopancreatobiliary (primary sclerosing cholangitis, cholelithiasis, portal vein thrombosis, drug-induced hepatotoxicity, and drug-induced pancreatitis), ocular (episcleritis, scleritis, uveitis, and conjunctivitis), renal (nephrolithiasis, obstructive uropathy, fistulization of the urinary tract, and secondary amyloidosis), and pulmonary (chronic bronchitis, subglottic stenosis, bronchiectasis, and bronchiolitis). There are no data if there is increased or decreased incidence of extraintestinal manifestations of UC or CD during pregnancy.

Both osteoporosis and vitamin D deficiency (including compensated deficiency states with normal calcium and high parathyroid hormone) are common in UC. The major risk factors for osteoporosis complicating UC are age, steroid use, and UC activity.

8.2.5.2 Emergent Presentation

As in nonpregnant UC population, there are several presentations that require emergent management: profuse intractable intraluminal mucosal bleeding leading to hemorrhagic shock, intestinal obstruction, bowel perforation with symptoms and signs of peritonitis, and toxic megacolon with progressive dilatation of the colon with increasing abdominal pain with abdominal distention with antecedent bloody diarrhea [230]. Nausea and vomiting can be present in both intestinal obstruction (where it is more exaggerated with feculent vomitus) and toxic megacolon.

Toxic Megacolon

Sometimes it is difficult to differentiate between large bowel obstruction and toxic megacolon. The previous clinical presentation is a clue to diagnosis. Prior to clinical deterioration, the patient has typical symptoms of UC (diarrhea, bloody or non-bloody, abdominal pain, fever) and progression of abdominal pain with colonic distention [230]. Physical examination can reveal localized guarding with rebound tenderness and diminished bowel sounds [205, 230, 231]. Similar signs can be found in the early phase of intestinal perforation, while in advanced bowel obstruction, bowel sounds are absent.

8.2.6 Differential Diagnosis

8.2.6.1 *C. difficile*-Associated Toxic Colitis

Historically, both peripartum *C. difficile*-associated disease and the disease during pregnancy have been considered an unusual occurrence and, when present, have generally been a mild disease. However, in 2005, a report [232] raised concern about a possible increase in both the frequency and severity of *C. difficile*-associated disease in pregnant women, including severe complications such as those resulting in intensive care unit admission, toxic megacolon, colectomy, death, and fetal loss. The pathophysiology of the infection in pregnancy remains poorly understood [233]. Although antibody production is generally increased during pregnancy, this production may not be specific or protective in severe CDI cases. The optimal management must include a low threshold for testing, early recognition, and close monitoring for signs and symptoms of deterioration, such as an increase in abdominal tenderness and distention, elevation of leukocyte counts over 20,000/mm^3, or a rising creatinine level [234]. A subtotal colectomy can be lifesaving in severe cases; indications for gastrointestinal surgery include dilated (>10 cm) intestinal loops, peritonitis, perforation, and persistent sepsis with a leukocytosis of more than 20,000/mm^3 [235].

8.2.7 Diagnosis

8.2.7.1 Elective Presentation

Diagnostic procedures are no different from usual during pregnancy. Interpretation of blood investigations for IBD during pregnancy can be difficult. Due to hemodilution, hemoglobin and albumin decrease as pregnancy progresses, and therefore they cannot be used in the assessment of disease activity. Iron deficiency is common because of chronic iron loss; this may be exacerbated during pregnancy; thus, a hypochromic, microcytic anemia is frequently present. Laboratory investigations should include full

blood count, urea and electrolytes (potassium, sodium, calcium, and magnesium), liver function tests and erythrocyte sedimentation rate or CRP, ferritin, transferrin saturation, vitamin B12, folate, and albumin.

A proctoscopic examination is suggestive of nonspecific inflammatory bowel disease or can show macroscopic changes characteristic for UC such as pseudopolyps or ulcerated hemorrhagic mucosa with pus and blood [231]. Biopsy should be taken for definitive diagnosis by pathohistological examination.

Ultrasound is used extensively in obstetric practice and is the safest form of radiological imaging. It can be used to assess abscess formation, as well as bowel wall thickness (as evidence of active inflammation). In addition, fetal status should be obtained.

Safety of colonoscopy and flexible and rigid sigmoidoscopy in pregnancy are confirmed (see Sect. 8.1.5.3). The future probably lies on capsule endoscopy in assessing mucosal inflammation in UC [236]. Currently, there are no studies on pregnant population, but there are many advantages due to the elimination of diagnostic radiography and contrast procedures and sedation for colonoscopy.

8.2.7.2 Emergent Presentation

Clinical examination is especially difficult in the third trimester of pregnancy due to enlarged gravid uterus and displacement of intraperitoneal organs. An additional difficulty is that physicians are reluctant to perform initial and repeated plain X-rays of the abdomen which would otherwise be done in nonpregnant patients if indicated. During less than 16 weeks of pregnancy, morphology and location of colonic dilation on plain abdominal X-ray are the same as in nonpregnant population (Fig. 8.4). Specific difficulty during the third trimester is displacement and sometimes distortion of small and large bowel making radiologic diagnosis more difficult (Figs. 8.5 and 8.6). In addition, it is difficult to measure colonic dilation in different colonic segments in the third trimester.

In unequivocal cases, abdominal CT (Fig. 8.7) is mandatory because it accurately predicts

Fig. 8.4 Plain abdominal X-ray in 16 weeks gestation showing a persistently dilated transverse colon with a diameter of 8 cm. Reproduced with permission from [237]

Fig. 8.5 Supine X-ray in 30 weeks of pregnancy. Gravid uterus displacing gas-filled colon without dilatation. Reproduced with permission from [238]

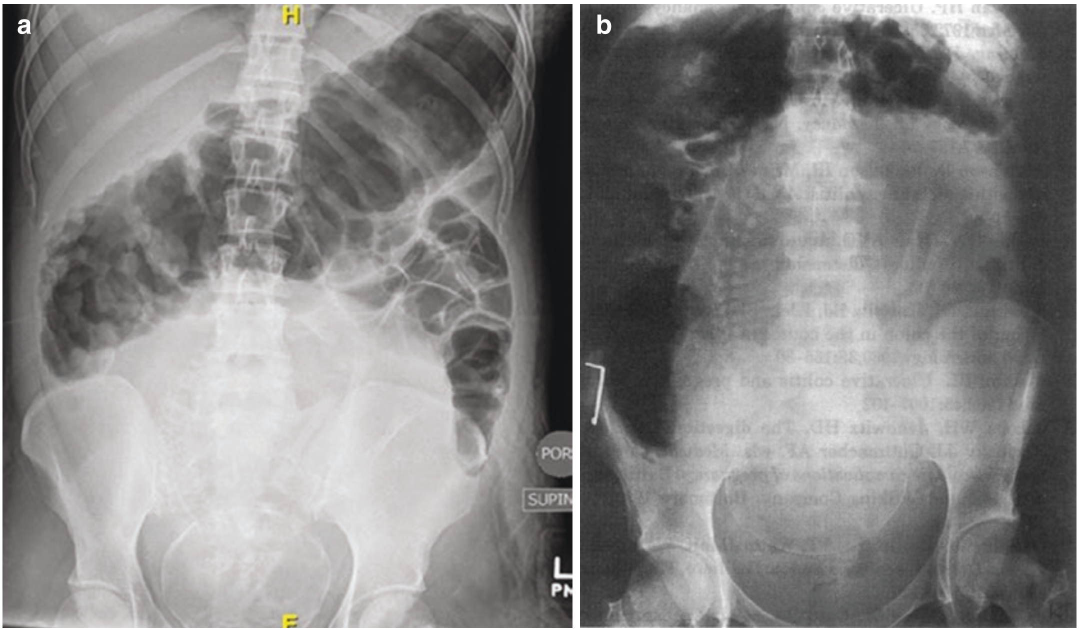

Fig. 8.6 Toxic dilatation of the colon in (**a**) 31st week. Reproduced from [230] under the CC BY Attribution License. (**b**) 33rd week of pregnancy. Reproduced with permission from [239]. Note the progressive bowel displacement as the gravid uterus enlarges

Fig. 8.7 Abdominal CT at 28 weeks gestation. Ascending colon diameter was 7.6 cm, transverse colon 9.2 cm, and descending colon 5.7 cm, which was consistent with toxic megacolon. Bowel wall thickness is normal without signs of ischemic changes. No abdominal free gas or effusion found. Reproduced with permission from [240]

colonic diameter, ischemic changes, or bowel perforation which determines conservative or surgical therapy [240].

8.2.8 Treatment

8.2.8.1 Medical Treatment

The medical prevention and treatment of toxic megacolon during the course of pregnancy should then follow the same prescriptions as for the non-pregnant patient. Although immediate colectomy without any trial of medical treatment was advocated for all cases of toxic megacolon in pregnancy by Holzbach in 1969 [205], 24–48 h of intensive medical treatment is also recommended [213, 222, 239, 241, 242]. Unfortunately, only 10% of patients responded well to medical treatment and gave birth to viable fetuses [222, 242]. The reported success rate of medical treatment in the nongravid state is similar [243]. Medical treatment of toxic megacolon during pregnancy raises the important question of the potential effects of drugs on the fetus (see Sect. 8.1.7.1). Due to possible effects of medications on the fetus and very low cure rate of toxic megacolon with medical treatment, it is questionable whether medical treatment for toxic megacolon due to UC is indicated. In addition, conservative therapy includes repeated plain abdominal X-rays or even abdominal CT which also have cumulative dosing effect on the fetus.

8.2.8.2 Surgical Treatment

Multiple procedures, ranging from diverting loop ileostomy to total proctocolectomy, have been described to treat fulminant and toxic UC in pregnant patients. Some have proved to be unsuitable. In general, population, before the 1950s ileostomy was the most commonly performed surgical procedure for toxic megacolon. However, this procedure produced unsatisfactory results because the dilated colon sometimes perforated despite the diversion. Mortality rates of 50–70% in general population were commonly reported—rates not much better than those that seen with medical therapy alone [244]. Proctocolectomy also is inappropriate in the acute situation because it is a long, complex operation and requires pelvic dissection, which may be difficult because of uterine enlargement and grossly dilated pelvic vessels. Moreover, increased manipulation of the gravid uterus increases the risk of spontaneous delivery and preterm labor.

Indications for Emergent Operation

During the 1980s, 2.3–3.9% of patients with UC during pregnancy required surgical intervention [207, 222]. Indications for emergent operation are the same as in general population: intractable hemorrhage, perforation, toxic colitis (toxic megacolon), and fulminant disease refractory to medical therapy. The timing of the emergent operation is also the same as in nonpregnant population. Duration of pregnancy is important for obstetric management (Fig. 8.8).

Turnbull "Blowhole" Procedure

In 1971, Turnbull et al. advised colonic decompression and diversion by blowhole colostomy and loop ileostomy for patients with toxic dilation of the colon to prevent perforation and sepsis in the severely ill patient [246]. Authors had recognized the risk of iatrogenic perforation and fecal spillage caused by the manipulation of the friable edematous colon during colectomy (especially in mobilizing the splenic flexure), which has a high mortality and morbidity rate. They believed that iatrogenic perforation is likely to occur and can be anticipated when the omentum is densely adherent to the colon. Indeed, occult sealed perforations can exist on the posterior aspect of the colon and become overt only when the colon is mobilized. Transmural penetrating ulcers are a feature of toxic dilatation of the colon and are "plugged" or sealed on their serosal aspect by omentum or adjacent viscera. Disrupting these seals results in fecal spillage. To avoid manipulating the colon, colonic decompression was advised and diversion in the form of a skin-level ("blowhole") colostomy and loop ileostomy. The procedure is contraindicated in the presence of a free perforation, abscess, and hemorrhage. Ooi et al. reported good success with Turnbull technique in two pregnant patients with toxic megacolon (Figs. 8.9 and 8.10).

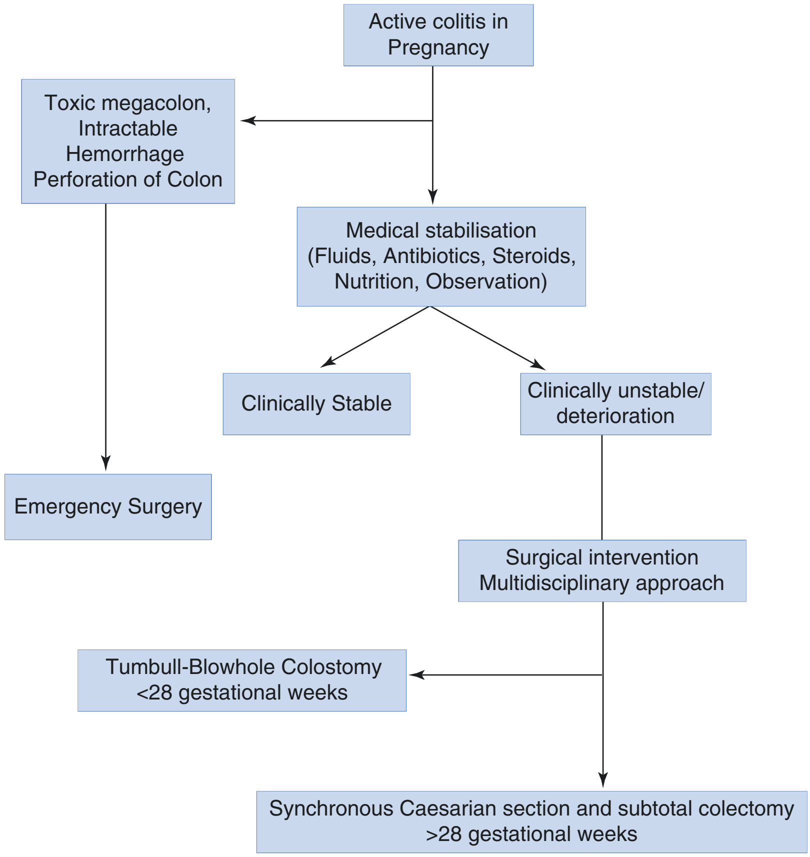

Fig. 8.8 Treatment algorithm for pregnant patients with ulcerative colitis. Reproduced with permission from [245]

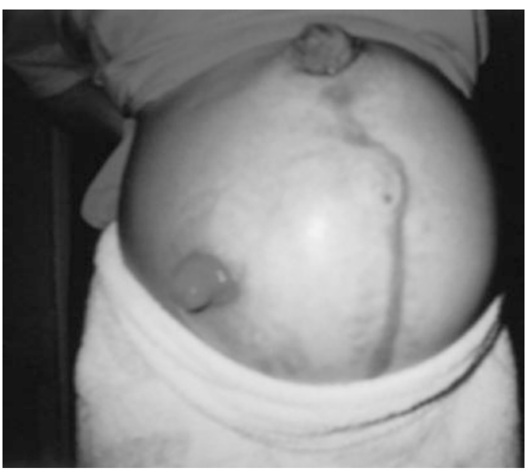

Fig. 8.9 The gravid patient with healed midline scar, loop ileostomy (to the right of midline), and skin-level transverse colostomy. Reproduced with permission from [237]

Fig. 8.10 The same patient after elective Cesarean section, showing a scaphoid abdomen with transverse colostomy and ileostomy and ready for definitive restorative proctocolectomy. Reproduced with permission from [237]

However, the large size of their uterus and minimal manipulation, rather than the severity of the colitis, is sometimes the deciding factor in the decision to undergo the blowhole procedure. These patients would have been candidates for (sub)total colectomy and ileostomy in the absence of pregnancy.

This procedure has the advantage of a short anesthesia time and minimal surgical trauma, which may dramatically improve outcome in extremely ill patients. The disadvantage of a blowhole colostomy is that the remaining colon may cause ongoing toxicity (severe hemorrhage, sepsis) requiring repeat operation leading to increasing risk to mother and fetus. Therefore, the Turnbull "blowhole" procedure is far less practiced currently. If performed, definitive surgery could then be performed 6 months later.

Total Abdominal Colectomy

In 1951, Crile and Thomas advised total abdominal colectomy and end ileostomy with preservation of the rectum for toxic megacolon [247]. Total abdominal colectomy, with preservation of the rectal stump and Brooke ileostomy, is the most commonly performed procedure for severely ill patients who require urgent or emergent colectomy for fulminant or toxic UC. It eradicates most of the disease and requires no bowel anastomosis or deep pelvic dissection while allowing the patient to be weaned from most medical agents. In addition, it does not preclude or compromise the results of subsequent IPAA [140, 248]. After colectomy, a decision should be made regarding the rectal stump. Stump breakdown and leakage leading to intra-abdominal sepsis is a major concern. The stump can be handsewn in two layers and wrapped with the omentum, and this is a safe procedure as long as the inflammatory process has not compromised the integrity of the bowel wall. Another option is to bring out the rectal stump as a mucus fistula. If a mucus fistula is to be placed, the remnant stump should be kept long. Because of the enlarged uterus, the stump will need to be brought out through an extraperitoneal plane deep to the broad ligament and dilated ovarian vessels. In advanced pregnancy bringing out the distal sigmoid colon as a mucous fistula would be hindered by the broad ligaments, draped across the abdominal cavity from the enlarged uterus [249]. Therefore, Hartmann's procedure with short rectal stump is an alternative. The rectum is irrigated with antiseptic solutions at the time of surgery to remove the excess bloody mucoid material and a rectal tube left in place to keep it decompressed in the postoperative period [140].

Rectal excision when indicated, for example, in intractable rectal hemorrhage, may be complicated by the need for hysterectomy. This is because of the risk of traumatizing the engorged pelvic veins leading to severe hemorrhage.

A stomal therapist should mark the patient before surgery.

> In pregnant patients, the optimal location for the stoma on the abdominal wall is usually higher than normal because the stoma will drop to a lower position after delivery.

Synchronous Cesarean Section and Subtotal Colectomy

According to previous reports, the majority of pregnant women requiring urgent surgery for UC have undergone metachronous colonic surgery and CS or vaginal delivery with a high maternal and or fetal morbidity and mortality. Only three cases have previously been reported where synchronous colectomy and delivery have taken place, two occurring at 32 weeks and one at 28 weeks gestation without maternal or neonatal morbidity or mortality [206, 241, 245].

8.2.8.3 Anesthetic and Perioperative Management

See Chap. 21.

8.2.8.4 Obstetric Management

Prevention and Treatment of Preterm Labor

See Chap. 23.

Mode of Delivery

Recommendations for CS are:

> - Acute abdomen in the late third trimester
> - IPAA (questionable)
> - Bowel or IPAA obstruction with a gravid uterus
> - Acute or chronic pouchitis

In patients presenting with acute abdomen, the treatment depends on the trimester of pregnancy.

During the first two trimesters, only surgical treatment of the cause of acute abdomen is treated. In the late third trimester, due to the high incidence of postoperative (during the first few days) spontaneous induction of labor, CS is recommended [140, 157]. After surgery without CS, fetal monitoring should begin in the postanesthesia recovery room, and the patient should be watched carefully for spontaneous labor.

IPAA alters the anatomy of the gastrointestinal tract, placing the pouch at risk from compressive obstruction by the gravid uterus. Induction of labor in a near-term fetus is a reasonable initial method of management preventing possible external compression on the IPAA and small bowel obstruction [215]. Patients with IPAA can have a normal vaginal delivery without fears of damaging the pouch or fissuring of the anal sphincter [250, 251]. Subclinical differences in anorectal physiology were however demonstrated as women with vaginal deliveries had significantly lower squeeze pressure on anorectal manometry and significantly more anal sphincter defects detected by anorectal sonography than those women with CS [151]. In general, anal sphincter function (daytime and nighttime stool frequency or continence) may be altered during the third trimester and immediate postpartum period, but its function typically returns to baseline in most patients, usually within 3 months after delivery [150, 250–252]. Although a few patients may have long-term disturbances in anal function, it appears unrelated to the method of delivery [252]. Damage to the anal sphincter may be compounded by aging, and the effects on the pouch will not be seen for several years. Functional IPAA outcomes with vaginal deliveries after IPAA were no different to those of women who did not have children after IPAA [253]. There is one case of successful decompression of IPAA compression by gravid uterus by emergent CS. The obstruction was proximal to IPAA [214].

There is no mention of the type of delivery when any form of pouchitis is present. The patient, the obstetrician, and the surgeon should discuss the theoretical risk to long-term pouch function depending on the mode of delivery.

Although the first report led to the recommendation that delivery should be performed by CS to avoid damage to the sphincter mechanism [254], later reports stated that the majority of pregnant women with an IPAA could deliver vaginally with episiotomies [148, 149]. In some cases, the technique of episiotomy had to be modified to a mediolateral position [231]. A cohort of 72% of colorectal surgeons believed that they should advise the patient on the optimal mode of delivery and not the obstetrician or the gastroenterologist [255]. Established risks of vaginal delivery, such as pouch and sphincter injury may result in fecal incontinence [147, 148, 150, 151, 256]. These concerns account for the higher preference of CS by colorectal surgeons (62%) [255]. However, this may be an unfounded concern which can lead to unnecessary recommendations for CS [150, 252, 257]. The national average for CS in general in the United States, independent of specific maternal medical issues, is already close to 32%. The unnecessarily increasing rate of CS places IPAA patients at a higher risk of documented complications associated with repeat CS [258]. CS has its own inherent risks [147, 252], and measures have been undertaken to decrease the rates of the first CS.

8.2.9 Prognosis

Early reports emphasized that the onset or exacerbation of symptoms during pregnancy was frequently fatal to both the mother and baby [259]. The preexisting renal disease probably played a large part in poor prognosis. Recent improvements in care mean that a safe outcome can usually be anticipated. Women with UC, which is symptomatic at the start of pregnancy, are likely to have symptoms throughout the pregnancy in spite of medical treatment [83].

8.2.9.1 Fertility and Sexual Health

Relationships, sexual health, and fertility in IBD patients are interrelated. UC does not affect fertility [22, 83, 207, 219, 220, 223, 260]. Other studies that found reduced fertility were probably flawed owing to short follow-up periods, patient

selection, and an inadequate medical control of the disease [221, 261] or inadequate numbers of patients observed [262]. Therefore, women with UC have fertility rates similar to the general population prior to surgery [83, 175, 176].

Fertility After Surgical Therapy

Surgery is negatively associated with fertility. While some reported no difference in fertility rates post-IPAA [176, 256], others showed a significant decrease in fertility rates (by as much as 80%) [263]. There is a threefold increase in infertility rate after an IPAA [264] with 38.6–48% of infertility rate in UC patients after IPAA versus 13.3–15% in UC patients managed nonoperatively [265, 266]. Patients who undergo a proctocolectomy with ileostomy also experience a reduction in fertility [267], as do patients with familial adenomatous polyposis who undergo IPAA [268]. The risk of infertility after IPAA should be discussed with the patient prior to surgery as one of the potential risks of the operation. Most likely, the greatest reduction in fertility is a result of (1) extensive pelvic dissection involved in creating the pouch, (2) the consequent adhesion formation in pelvis causing Fallopian tube scarring and occlusion, and (3) direct damage to the reproductive organs. Although not proven, some recommend encircling the ovaries and tubes with anti-adhesion membranes at the time may reduce the incidence of peritubal adhesions [269], potentially improving fertility. A potential option for some patients may be an ileorectal anastomosis, which preserves fertility [270]. It is unclear if techniques such as subtotal colectomy with rectal stump and ileostomy during the childbearing years and then creating an IPAA later in life are helpful in reducing infertility rates. The drawbacks of the latter procedure include rare ileostomy complications during pregnancy such as obstruction and stoma-related problems [271], technical difficulties in creating a functioning pouch several years after the initial surgery, and the patient's reluctance to have a long-term ostomy. Recent studies show that total laparoscopic colectomy with IPAA causes significantly lower infertility rates compared to the open approach [269, 272, 273].

"Easier" decision is when an acute abdomen is present with an absolute indication for emergent operation. In such cases, it is a lifesaving operation, and fertility is then only the third goal after a mother and fetal outcome. In a study by Anderson et al., 50% (2/4) of operated patients due to toxic megacolon developed severe postoperative pelvic and subphrenic abscesses. Three patients had difficulty conceiving or secondary infertility since the surgery. The social morbidity as a result of this was high divorce rate (3/4) [239]. Despite the problems encountered during pregnancies, it is interesting to note that each of these patients has tried (and two have succeeded) to become pregnant again, albeit generally by a different husband.

In conclusion, In UC overall fertility rates are normal [264, 274] except after surgical resection with IPAA [257, 263, 266, 275]. Estimated risk of infertility after IPAA is increased by a factor 3 [265]. Colectomy with ileorectal anastomosis [270] or subtotal colectomy with an ileostomy and pouch creation after childbearing [116] may be reasonable alternatives for women wishing to become pregnant [116, 276]. Laparoscopic IPAA could reduce adhesions and may be a suitable alternative for patients of childbearing age [269, 272, 273].

8.2.9.2 Pregnancy Outcomes in General

> The disease severity at the time of conception plays a major role in the outcome. For patients who want to conceive, the ideal timing is when UC is in remission.

UC occurring for the first time during pregnancy has previously been considered dangerous, with a maternal mortality rate of 15% [239]. In years past, the risk to the mother was considered so high that therapeutic abortion was advocated if severely active disease occurred during pregnancy [20]. Currently, prompt and aggressive medical therapy is the first line of treatment and has the best chance of halting disease progression. Today, among completed pregnancies,

84% produced normal full-term babies, and 77% resulted in uncomplicated vaginal delivery; low birth weight and postmaturity were no more common than usual. Even when UC first developed during pregnancy, there was a good chance (88%) of a normal live birth [83]. In contrast to CD, women with UC had similar rates to controls of preterm delivery, LBW, and small for gestational age infants but a significantly higher rate of congenital malformations (7.9% vs. 1.7%) [186]. The study did not account for medication use, and the results have not been replicated in other studies. The studies that reported on congenital abnormalities did not distinguish between the major and minor malformations; one study included chromosomal disorders [186], which may result in overestimation of the risk. The *Hungarian Case–Control Surveillance* of congenital anomalies (1980–1996) reported the odds ratio of congenital anomalies in UC patients vs. controls of 1.3 (0.9–1.8), adjusted for parity, age, and medication use [277]. A meta-analysis showed a normal pregnancy in 76–87% of patients. Fetal malformations were observed in about 1% of all pregnancies, and the frequency of spontaneous abortions and stillbirths was similar to that observed in the general population [194].

Patients with UC have similar rates of CS as normal pregnant population [145]. Only patients with IPAA have a higher rate of elective CS. No data exist whether the outcomes of the infants differed after vaginal delivery and CS.

Predictors of poor outcome (preterm birth, LBW, intrauterine growth retardation, small for gestational age, congenital anomalies, Apgar scores, stillbirth, and complications of labor) were significantly higher having IBD, either UC or CD and having had surgery for IBD [184]. In the studies from the 1980s, disease activity at conception was associated with a higher rate of fetal loss [33] and preterm birth [78]; disease activity during pregnancy was associated with LBW and preterm birth [185–188]. One hypothesis is that an increase in circulating prostaglandin levels during a flare could initiate preterm labor with the induction of smooth muscle contraction [190, 191]. Another theory is that the role of increased gut permeability during increased inflammation could alter nutritional and immunological factors affecting labor [190].

Conversely to CD, smoking in UC women does not increase their risk of preterm delivery [278]. However, given the known risk of smoking on the individual and the baby, smoking cessation should be encouraged in all scenarios.

8.2.9.3 Pregnancy Outcomes After Surgery

Elective Surgery

Surgery is to be avoided as far as possible because earlier reports claim that colectomy in pregnancy has been previously reported to carry a 60% risk of inducing spontaneous abortion. In the period between 1951 and 2004, a total of 37 cases were reported [20, 79, 157, 205, 206, 208, 209, 237–239, 241, 249, 279–281]. Overall, the fetal and maternal mortality was 49% and 22%, respectively. The majority of maternal and fetal mortality seen was found in cases reported before 1987. From 1951 to 1987, the fetal and maternal mortality was 67% and 24%, respectively. Similar outcomes up to 1987 were found by another study with 35 cases (fetal mortality 53%, maternal mortality 29%) [239]. While maternal death is becoming less frequent, the high stillbirth rate probably reflects the severity of the disease rather than the effects of the operation. After 1987, the fetal and maternal mortality was zero, and the postoperative morbidity was negligible.

Finally, two studies showed in patients with IPAA pregnancy caused a small increase in nocturnal stool frequency [148, 231].

Breastfeeding per se is recommended for at least 6 months after birth (see Sect. 8.1.8.3).

Emergency Surgery

Higher fetal mortality is found during and after emergency surgery during pregnancy. A review in 1972 by Becker of the surgical treatment of toxic megacolon in pregnancy revealed maternal mortality of 36% and fetal mortality of 100% [242]. Up to 1986, there were 35 cases in the literature [20, 79, 205–213, 241, 242] with the overall maternal mortality rate of 29% and the

fetal mortality rate of 53%. In 1990 reported maternal mortality was 21% and fetal mortality 71% [231], while Anderson et al. in 1987 reported 50% fetal mortality [239]. Up to 2014, there were 38 cases of UC managed by surgical intervention during pregnancy published [140, 282]. Surgical intervention coincided with CS or vaginal delivery in 42%. In the group where pregnancy continued, 59% were in their second trimester. Twenty-one procedures were documented in 20 women: 14 women underwent subtotal colectomy and ileostomy, 1 woman had total colectomy and ileostomy, 4 women had a colostomy and ileostomy, and 1 patient each underwent terminal ileostomy and transverse colostomy alone. All cases of maternal and mortality were reported prior to 1974 [282]. While maternal death is becoming less frequent, the high stillbirth rate probably reflects the severity of the disease rather than the effects of the operation.

Today, maternal survival with toxic megacolon due to UC is almost 100%. In the only case with maternal mortality, initially more aggressive surgery (subtotal colectomy as initial operation) would probably result in maternal survival. Up to 1969 fetal mortality was 100%, while, interestingly, after 1972 fetal survival was 100% (Table 8.4). This implies that even toxic megacolon as a serious complication and subtotal colectomy as the extensive operation result in both maternal and fetal survival of 100%.

Earlier reports of emergency colectomy for severe UC claimed high maternal and fetal mortality rate of 53% and 29%, respectively [286]. Newer studies show no maternal and fetal mortality performing emergency colectomy [245].

Table 8.4 Outcome of toxic megacolon in pregnancy

Authors	Year	Gestation (weeks)	Maternal surgery/outcome	Fetal outcome
Marshak et al. [209]	1960	24–28	Subtotal colectomy/alive	Preterm labor, 29 weeks/dead
Peskin and Davis [208]	1960	24	Transverse colostomy/alive	Unknown
Holzbach [205]	1969	27–30/2d postpartum	Subtotal colectomy/alive	Preterm labor, 30 weeks/died after 18 h
		22–23	Colostomy and ileostomy then subtotal colectomy/died after 5 months	Preterm labor, 24 weeks/dead
Becker [242]	1972	22–24	Conservative therapy/alive	Vaginal, 7 months/alive
Cooksey et al. [213]	1985	24–25	Subtotal colectomy/alive	Elective CS, 34 weeks/alive
Anderson et al. [239]	1987	28–33	Subtotal colectomy/alive	Vaginal delivery, 34 weeks/alive
Watson and Gaines [157]	1987	28	Subtotal colectomy/alive	Vaginal delivery/alive
Hashim and Belliveau [283]	1998	19	Subtotal colectomy/alive	Preterm labor 25 weeks/alive
Soin et al. [284]	1998	19–21	Subtotal colectomy/alive	Vaginal delivery at term/alive
Ooi et al. [237]	2003	16	Turnbull blowhole colostomy and loop ileostomy/alive	Emergent CS, 36 weeks/alive
		10	Turnbull blowhole colostomy and loop ileostomy/alive	Elective CS at term/alive
Toiyama et al. [249]	2004	8–12	Subtotal colectomy/alive	Vaginal delivery at term/alive
Orabona et al. [240]	2015	27–28	Colonoscopic decompression/alive	Emergent CS 28 weeks/alive
Quddus et al. [230]	2015	26–31	Subtotal colectomy/alive	Emergent CS, 31 weeks/alive
Uchino et al. [285]	2015	12–23	Subtotal colectomy/alive	Emergent CS, 23 weeks/alive
		11–15	Subtotal colectomy/alive	Vaginal delivery, 36 weeks/alive

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9 Spleen

Abstract

Almost all surgical complications related to spleen during pregnancy include significant intraperitoneal bleeding. The symptoms commonly include acute and severe abdominal pain with progression to hypovolemic shock. The problem is that these patients do not have any underlying disease or did not have similar symptoms previously. If abdominal trauma is not the cause, abdominal sonography rarely finds the cause of free intraperitoneal fluid. Emergency exploration is the mainstay of therapy to find the cause and stop the bleeding. Currently, interventional radiologic techniques are used to stop splenic bleeding if diagnosed, with the advantage of avoidance of surgical operation. If interventional radiologic techniques are not successful, surgery for the cessation of bleeding, commonly in a form of splenectomy, is the ultimate measure. The diagnosis of splenic bleeding and intervention should be made early to save not only the fetus but also the mother.

9.1 Splenic Rupture

9.1.1 Definition and Historical Perspective

Splenic rupture can occur with any degree of trauma to a normal spleen or minimal trauma to a diseased spleen. Eastman and Hellman made three important statements with respect to rupture of the spleen in pregnancy [1]:

- The rarity of the condition
- The danger of confusing it with obstetric complications
- The importance of preexisting disease of the spleen

The first case of a splenic rupture in pregnancy was reported by Johannes Sylvester Saxtorph (Fig. 9.1) in 1803 [2]. In 1866 Simpson referred to three cases of fatal rupture of the spleen which had occurred, respectively, in the pregnant, parturient, and puerperal state. He pointed out the circumstance that, during pregnancy, there is often, if not generally, a kind of normal or physiological leukocytosis. A certain amount of softening very frequently accompanies the hypertrophy of the spleen and predisposes to the laceration of the organ under strong exertion and muscular effort, blows, etc. [3]. One of the earliest cases was by Hubbard in 1879, but the authenticity of this report is open to question as the findings are not recorded too clearly or soundly [4]. Kotschnew and Manankow gave the first overview of splenic rupture in 1930. The first nine cases were confirmed through autopsies. In 1958, Sparkman provided an overview of 44 recorded cases, with a detailed analysis of their etiology [5]. In 1967, Buchsbaum added an additional 27 cases to the list [6]. The literature up to 2003 indicates 18

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_9

more, bringing the total up to 89 [7]. Classification is made according to the cause [5]:

- Traumatic
- Following antecedent disease
- Associated with toxemia of pregnancy
- Spontaneous

Incidence according to the cause is presented in Table 9.1.

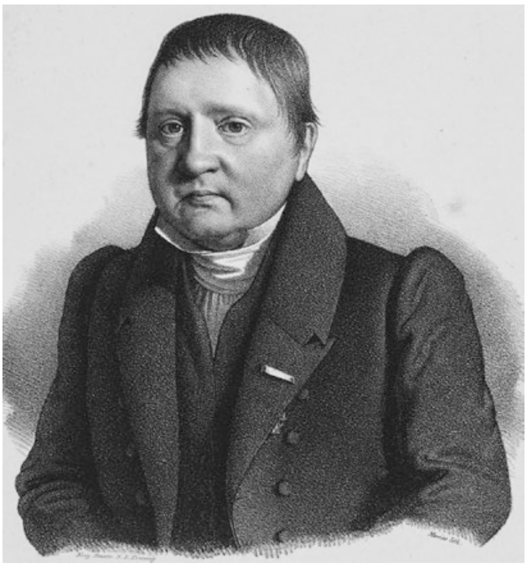


Fig. 9.1 Johannes Sylvester Saxtorph, Danish obstetrician (1772–1840), made the first description of the splenic rupture during pregnancy in 1803. Cropped picture from *Statens Museum for Kunst*, lithography by David Monies in 1835. Reproduced with permission

Table 9.1 Pregnancy-related causes of splenic rupture

Etiology	Incidence (%)
Normal pregnancy	58
Splenic ectopic pregnancy	24
Post-vaginal delivery	5
Post-Cesarean section	5
Preeclampsia	2.5
Ruptured ectopic pregnancy	2.5
HELLP syndrome	2.5

Reproduced with permission from [8]

9.1.2 Classification

9.1.2.1 Trauma

Etiopathogenesis

In its position behind the rib cage, cushioned under the left hemidiaphragm, the spleen is protected from most forms of direct trauma. The pathogenesis of rupture has been explained by Schamaun as a countercoup mechanism in which the spleen, because of its relative mobility, is driven against the vertebral column and ruptures [9]. Another mechanism explains the rupture on the basis of the ligamentous suspension of the spleen, which allows a limited degree of motion and then sudden fixation and laceration. Schonwerth described the deep inspiration at the instant of trauma (the fright mechanism) displacing the superior pole downward, while the lower pole is relatively fixed by the phrenicocolic ligament causing flexion of the spleen. Trauma over the rib cage then results in a capsular laceration on the stretched convex surface [10]. Sometimes underlying pathology and minor (repeating) trauma are unknown or unrecognized. In cases of previously changed spleen or additional pathology, even a minor or minimal but repetitive trauma is sufficient for splenic rupture. In one case, the prominent exostosis arising from the tenth rib had roughened and thickened a circumscribed area of the splenic capsule (Fig. 9.2) over the years as a result of the respiratory excursions and movement of daily life. Laceration of the unthickened lower pole finally occurred during pregnancy, at a time when splenic size, vascularization, and position may be altered [11]. In two cases, the initially spontaneous splenic rupture was diagnosed, but cavernous hemangioma of the spleen as the source of hemorrhage was confirmed. It may be that minor trauma was the precipitating factor [12, 13].

Specific etiology is complicated delivery where the spleen can be traumatized [14] (see Sect. 9.1.2.4).

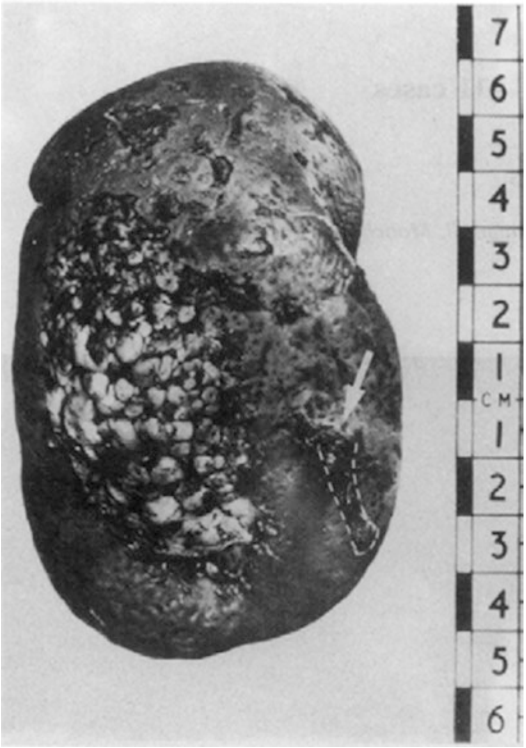


Fig. 9.2 The convex surface of the spleen to show the roughened capsule. The exostosis (*dotted outline*) has been replaced in the laceration (*arrow*). Reproduced with permission from [11]

9.1.2.2 Toxemia of Pregnancy

This classification was introduced by Sparkman in 1958 because a number of cases were associated with toxemia of pregnancy [5]. The authors suggested that toxemia may be associated with specific changes, such as hypertension, thrombosis, and diffuse angiitis, which may predispose toward vascular or visceral rupture [15–19].

9.1.2.3 Underlying Splenic Disease

Cases have been reported associated with malaria [20], Banti's syndrome [21], hemangioma [22], subacute bacterial endocarditis [23], leukemia and other blood-related disorders [24], and typhoid fever [25]. Buchsbaum reported spontaneous rupture in four cases—hemangiomas were present in two and splenitis in another two [6].

The complete list of underlying causes of spontaneous splenic rupture is the same as in non-pregnant population. It includes local splenic disorders, such as splenic cysts and diffuse angiomatosis; hematologic diseases, such as hemophilia, congenital afibrinogenemia, and hemolytic anemia; metabolic disorders, such as amyloidosis, Wilson's disease, Gaucher's disease, and Niemann-Pick disease; drug induced, such as intravenous heparin, warfarin, and streptokinase; iatrogenic causes, such as extracorporeal shock wave lithotripsy and clamping of the portal triad; and miscellaneous, such as vomiting, uremia, systemic lupus erythematosus, and other connective tissue diseases. Most notable are the infectious causes, such as infectious mononucleosis, which is considered the most common cause of the spontaneous splenic rupture, as well as malaria [26].

9.1.2.4 Spontaneous Rupture of Normal Spleen

Definition

Opinion is divided as to whether the normal spleen ever ruptures spontaneously. Some authors deny the possibility, while others accept it as a rare occurrence [27]. Nelson and Hall reported a markedly diminished and almost total absence of germinal centers in lymph nodes of pregnant women at term [28]. Of all cases of splenic rupture in pregnancy, only 2.2% were spontaneous in the puerperium [16]. In 1958, Orloff and Peskin established the following four criteria for the diagnosis of spontaneous rupture of a normal spleen [29]:

- No history of trauma
- No systemic disease that can affect the spleen
- No evidence of perisplenic adhesions to suggest previous trauma
- Splenic parenchyma, vasculature, and capsule normal macroscopically and histologically

A similar definition is by Sparkman [5]. More frequent examination of the surgical specimen

will reveal pathologically changed spleens. The high incidence of secondary rupture indicates that as adequate histories are obtained and reported, more cases of minor trauma forgotten by the patient during the long-latent period will be revealed [6]. It is likely that the so-called spontaneous rupture, in fact, occurs as a result of capsular injury by the lower ribs from trivial blunt trauma (for instance, coughing and straining) either unnoticed by the patient at the time or forgotten since in the light of subsequent events [29]. These factors will markedly lower the number of cases designated as spontaneous rupture of the normal spleen in pregnancy. Sheehan and Falkiner in 1948 analyzed 163 routine obstetric necropsies and found that in the three following clinical conditions, the spleen was commonly enlarged (>200 g) in the second half of pregnancy [30]:

- Severe anemia of pregnancy
- Accidental hemorrhage of the abruption type
- Puerperal thrombophlebitis or gross septic endometritis

This enlargement is an important risk factor for the splenic rupture.

Incidence

Zuckerman and Jacobi reviewed the world literature up to 1937 and collected 28 such cases, regarding 21 of these as genuine spontaneous rupture of the normal spleen and 7 as doubtful [31]. Another 21 cases of spontaneous rupture of a normal spleen during pregnancy or labor have been reported in the English language literature between 1958 and 2011 [32]. However, a spontaneous rupture in pregnancy without antecedent trauma is rare and occurs most commonly in the third trimester or puerperium [15, 32].

Pathophysiology

The pathogenesis includes several mechanisms of rupture of the spleen [33]:

- Local lesions as points of weakness
- The increase of capsular tension due to hyperplasia and engorgement
- Hypervolemic state
- Diminished peritoneal cavity volume,
- Compression by the abdominal musculature,
- Increased intra-abdominal pressure

However, the authors are unable to postulate any one theory as to the etiology of spontaneous rupture of the normal spleen. Therefore, it is obvious that minimal internal trauma, such as straining for a bowel movement, coughing, vomiting, sneezing, jumping, or even coitus [34] in the latter stages of pregnancy may be causally related to splenic rupture by increasing intra-abdominal pressure, which is then transmitted to a number of intra-abdominal organs. In addition, the hemodynamic changes that accompany pregnancy may predispose to spontaneous splenic rupture via two possible mechanisms. First, the combined effects of the increased circulating blood volume and reduced volume of the peritoneal cavity due to the expansion of the gravid uterus with disturbance of the normal position of the spleen, particularly where the splenic pedicle is short, make the spleen more fragile and therefore more vulnerable to rupture [35]. In keeping with this hypothesis, it is interesting that almost all cases have occurred in multiple pregnancies or in the third trimester of pregnancy. Secondly, circulating hormones such as estrogen and progesterone cause structural changes to the spleen that may increase the risk of splenic rupture during pregnancy even after minor trauma [36]. In earlier works, pregnancy was thought to predispose the spleen to rupture. Therefore, pregnancy was listed as an etiological factor in splenic rupture. This view completely disregarded Barcroft's work, in which he demonstrated on a small number of dogs that the exteriorized spleen shrinks markedly during pregnancy [37]. Furthermore, examination of the spleen at autopsy in eight pregnant female dogs with normal spleens failed to reveal any correlation between splenic weight and duration of pregnancy. Another widely held theory is that rupture of a small intrasplenic aneurysm may occur, with all traces of an aneurysm being destroyed by the hemorrhage, thus preventing its discovery by the pathologist.

9.1.2.5 Postpartum Splenic Rupture

Incidence

To date, only eight cases of spontaneous postpartum splenic rupture are reported in the literature [15–19, 38]. There are also several cases during labor [2, 39].

Etiopathogenesis

The etiology of spontaneous postpartum splenic rupture remains speculative at best.

Splenic Enlargement Per Se

It has been suggested that splenic enlargement and increased blood volume normally seen in pregnancy in addition to the trauma of parturition could be implicated in the pathogenesis of some cases of splenic rupture (Fig. 9.3), but this is controversial.

Blunt (Internal) Trauma

Suggested etiological factors in cases of true spontaneous rupture include blunt internal trauma, as proposed by Barnett (i.e., occasioned by coughing, vomiting, coitus in the latter stages of pregnancy, and the bearing-down efforts of the second stage of labor) [14, 40]. Several authors have suggested a short splenic pedicle or deeply recessed location of the spleen as congenital factors that might contribute to rupture by compressing the diaphragm during coughing, sneezing, or vomiting [29]. Whether the episode of tonic-clonic seizure that occurred in one case could be considered traumatic enough to induce injury to the spleen will remain unanswered [41].

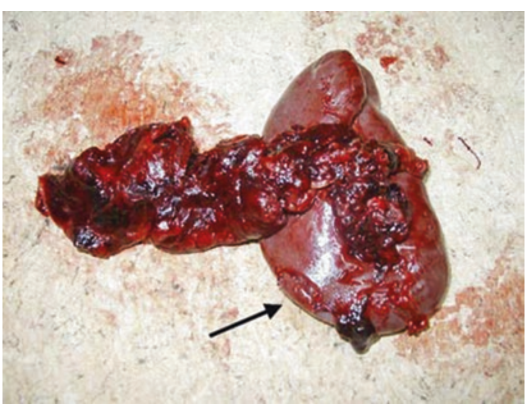


Fig. 9.3 Rupture of splenic capsule (*arrow*) on the lower pole. Reproduced with permission from [7]

Intrasplenic Aneurysm

Another widely held theory is that rupture of a small intrasplenic aneurysm may occur, with all traces of an aneurysm being destroyed by the hemorrhage, thus preventing its discovery by the pathologist. Larger aneurysms of the splenic artery are more prone to rupture during pregnancy, and even spontaneous rupture of the splenic vein has been reported.

Cesarean Section

At the operation, traction with undue force with sharp- or blunt-edged instruments during CS and insertion of packs could cause abrasive injuries to an already congested organ such as the spleen, especially in previously operated patients with intraperitoneal adhesions. Excessive force in exploring the upper abdomen and manual expression of the fetus by forceful pushing on the upper abdomen at the time of CS or even while removing clots from the paracolic gutters might lead to splenic injury, especially in those with high blood pressure [38].

Rapid Plasma Expansion

It might also be possible that rapid plasma expansion with blood products and other volume expanders could result in a rapid volume increase within the spleen, predisposing it to rupture [41].

9.1.3 Clinical Presentation

9.1.3.1 Medical History

When the patient has been involved in some obvious and serious accident and when there is associated bony and soft tissue injury (the most common is fracture of ribs, which occurs in 35% of cases of traumatic rupture of the spleen in the general population), it is frequently obvious that intraperitoneal bleeding has taken place. In some instances, the date of the accident may be remote

from the time of admission and may, under some circumstances, be forgotten altogether. In approximately 40–50% of cases of rupture of the spleen, no history of trauma is obtained.

9.1.3.2 Physical Examination

Rupture may become manifest:

- *Immediately* following the trauma
- *Delayed* and only recognized following a latent period

The immediate rupture usually presents no problem in diagnosis. The significance of the delayed form of rupture of the spleen was first emphasized in the general population by McIndoe in 1932 [42]. He reported that the acute onset of symptoms of rupture must occur 48 h or longer following the original injury if it is to be called *delayed* rupture. In many cases, the latent period exceeds 1 week.

Kehr's sign presents diaphragmatic irritation referred to the left shoulder tip region, and some claim it is almost pathognomonic when present with blunt abdominal trauma. Blood from any cause in the left subphrenic space causes positive Kehr's sign, and the most common are a splenic rupture and ectopic pregnancy. Kehr's sign is present in a small minority of these patients.

> The classic triad of epigastric pain, tenderness, and Kehr's sign in addition to blunt abdominal trauma is characteristic of a ruptured spleen.

Pain and tenderness are common. Epigastric pain is the symptom most commonly and most consistently reported. In some cases, there is an associated episode of vomiting. The pain is made worse on coughing, deep breathing, and moving. At rest, the pain may be almost completely relieved. The progressive severity of pain is common. In most cases, pain that was well tolerated at rest becomes more severe, and analgesic medication is requested. In a few cases, dyspnea is reported due to the expanding intraperitoneal mass, to declining circulating blood volume, or to loss of hemoglobin. Dullness on percussion over the left upper quadrant is an important sign. The enlarging uterus makes percussion and palpation of upper abdominal masses more difficult. Barnett states that in pregnancy, the enlarged gravid uterus does not give rise to *Ballance's sign* [40]. It is dullness to percussion in the left flank/left upper abdominal quadrant and shifting dullness to percussion in the right flank. The dullness in the left flank is due to coagulated blood, the shifting dullness on the right on altering position due to fluid blood. In later stages, the pain can become generalized, with distention and rigidity. Muscle spasm may not be present even in the presence of intraperitoneal blood. Eventually more than half of the patients will suffer hemorrhagic shock if the condition is left untreated [16]. Some authors have noted the confusing coexistence of hypertonicity of uterine muscle. Whether this is due to local peritoneal irritation is not known.

Postpartum Splenic Rupture

Rupture of the spleen in the postpartum period poses a significant difficulty for early diagnosis because of more common entities present with similar clinical findings especially early in the course of the rupture. This differential diagnosis should be kept in mind when external compression of the uterine fundus is done during vaginal delivery.

9.1.4 Differential Diagnosis

9.1.4.1 Pregnancy

In the first trimester, it is usually confused with ruptured ectopic pregnancy (Table 9.2). In the last trimester, placental abruption and rupture of the uterus are the two most likely differential diagnoses. However, in the case of rupture of the spleen, the uterus is not tender or hard, and fetal heart sounds can usually be heard (before hemorrhagic shock ensues).

9.1.4.2 Puerperium

Differential diagnoses include exaggerated postpartum pains, uterine rupture, intra-abdominal bleeding in general, and injury of a viscus (Table 9.2).

Table 9.2 Differential diagnosis of splenic rupture during pregnancy

Traumatic	Spontaneous			
	First trimester	Second trimester	Third trimester	Puerperium
Liver rupture	Ruptured ectopic pregnancy		Placental abruption	Postpartum pain
Uterine rupture			Uterine rupture	Uterine rupture
Renal rupture			Acute pancreatitis	Acute pancreatitis
			Renal artery rupture	Postpartum bleeding

9.1.5 Diagnosis

The true rate of preoperative diagnosis is unknown. One of the reasons for the complicated diagnosis is the unclear etiology of rupture itself. The frequency of correct diagnosis during the 1950s varied between 14% and 25% [5, 43].

Perhaps the most confusing in the later months of pregnancy is the finding of uterine tetany, suggesting the strong possibility of placental abruption. The presence of hemoperitoneum and peritoneal irritation may make adequate uterine palpation difficult and auscultation of fetal heart sounds uncertain. Albuminuria may be present and add further to the difficulty of distinguishing between intraperitoneal bleeding due to splenic rupture and that due to placental abruption.

Diagnosis is frequently difficult because the presence of the pregnancy leads the obstetrician to concentrate on the possibility of uterine or adnexal injury. The clinical symptoms and signs normally associated with intraperitoneal bleeding may be poorly defined. When blood is lost swiftly and in large amounts, all of the characteristic features of hypovolemic shock are recognized without difficulty; however, when blood loss is slower and smaller in quantity, the appropriate abdominal findings may be obscured. The diagnosis of spontaneous postpartum splenic rupture was not considered in either case preoperatively, even though there was no doubt as to the need for immediate surgical intervention and transfusion. Signs and symptoms of severe shock states might be mimicked by septic shock, amniotic fluid embolus, pulmonary embolus, cardiogenic shock, and disseminated intravascular coagulopathy.

9.1.5.1 Paracentesis

Before the era of the ultrasound and CT, paracentesis was used to diagnose intraperitoneal bleeding. The necessity of performing paracenteses in the four abdominal quadrants with a no. 18 needle has been strongly emphasized by Wright and Prigot; in 87% of patients with splenic rupture in the general population, the blood was obtained [43]. Dependence on the paracentesis has been criticized with statements that false taps lead to dangerous, sometimes mortal delay [43]. A repeat paracentesis is mandatory if doubt exists as to the cause of the patient's symptoms, or even better option is to proceed with laparotomy [43]. Currently, it is not used, especially in pregnancy where there is an additional possibility of uterine and amniotic sac injury with its consequences.

9.1.5.2 Plain Abdominal X-Ray

The radiographic examination is not of much value in diagnosing rupture of the spleen. Careful observation may indicate:

- Elevation of the left hemidiaphragm
- Displacement of the gastric shadow to the right
- Subphrenic opacity in the left upper quadrant
- The descent of the left part of the transverse colon

These signs are less useful in the third trimester because of physiological displacement of intraperitoneal organs by the enlarged uterus.

9.1.5.3 Transabdominal Ultrasound

Currently, transabdominal ultrasound is an inexpensive and practical way to obtain a quick diagnosis of intraperitoneal fluid accumulation or hematoma, which can be performed at the

patient's bedside or in the emergency unit [44]. This can aid in the initial workup of a patient with hemodynamic instability and abdominal distention, especially if exploration is contemplated or if CT is not feasible. Free fluid in the upper abdomen or left upper quadrant should raise suspicion of splenic rupture [45, 46].

9.1.5.4 Angiography of the Abdominal Aorta

In most cases, preoperative diagnosis of splenic rupture or rupture of the SAA is not known. In a suspected unruptured SAA, the gold standard for the diagnosis is arteriography [47], although ultrasonography and pulsed Doppler are preferable in pregnancy [48].

9.1.5.5 Abdominal CT

Native abdominal MSCT scan especially with i.v. contrast can define SAA with or without rupture preoperatively but is almost never used in pregnancy, as well as angiography. Abdominal CT scan is used when MRI is not available in emergency settings (Fig. 9.4).

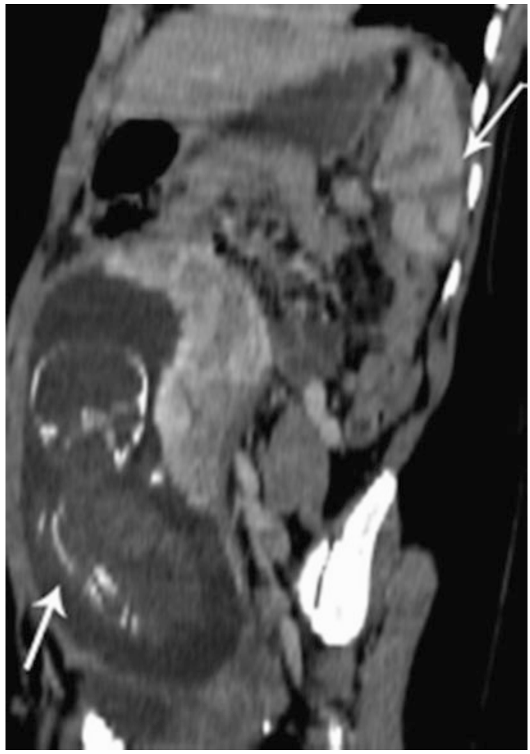


Fig. 9.4 An oblique sagittal reformatted CT scan image showing traumatic splenic laceration (*right arrow*) and the 26-week fetus (*left arrow*). Reproduced with permission from [49]

9.1.5.6 Diagnostic Exploration

Sometimes the cause of the hemorrhage is not known preoperatively, especially when the patient presents with hemodynamic instability. In such cases, laparotomy is the preferred because laparoscopy cannot define and stop all causes of bleeding especially in pregnancy and in hemodynamic instability.

9.1.6 Treatment

9.1.6.1 Historical Perspective

Splenectomy for ruptured spleen in pregnancy was first performed by Savor in 1898 [50]. The patient survived and delivered a full-term infant 3.5 months later.

9.1.6.2 Conservative Treatment

Conservative approach with close hemodynamic monitoring has been advocated in well-selected cases, most of which are traumatic in origin. There are no criteria for pregnant patients, but to be eligible for nonoperative management, patients should meet several criteria based on data on general population [51]:

- Hemodynamic stability
- The absence of peritoneal signs
- The absence of other abdominal injuries requiring surgery

Factors that predict failure of conservative measures in the general population include [51]:

- Preexisting splenic disease
- Age older than 55 years
- High-grade injury
- Significant hemoperitoneum
- Contrast blush in the spleen (suggesting false aneurysms) on CT

9.1.6.3 Surgical Treatment

Postpartum Splenic Rupture

The standard of care for patients with spontaneous postpartum splenic rupture remains emergency splenectomy. The survival rate of pregnant patients with splenic rupture who underwent splenectomy is 95.4%, compared with a 0% in patients who did not undergo splenectomy [16].

> The survival of patients with spontaneous postpartum splenic rupture rests on aggressive transfusion management, early diagnosis, and emergency splenectomy.

Operative Principles

Consideration should be given to performing a midline or paramedian (if the diagnosis is known preoperatively) vertical incision to facilitate access and visualization. The problem is that the patient is often seen first by the obstetrician, with a diagnosis of pelvic pathology, and the most common incision is a lower midline or Pfannenstiel incision. In cases of spontaneous rupture of the normal spleen, 75% of the cases that resulted in splenectomy were opened through an inadequate incision [29]. Some patients needed extensions, some a new incision, and in the balance, the surgery was made extremely difficult by the original incision. The diagnosis of spontaneous postpartum splenic rupture was not considered in either case preoperatively, even though there was no doubt as to the need for immediate surgical intervention and transfusion. Therefore, compulsory evaluation of the entire abdomen in posthysterectomy hemoperitoneum is advisable. CS in patients with intraperitoneal bleeding due to splenic rupture may serve one of two purposes. In some patients, adequate surgery for the ruptured spleen cannot be undertaken until the uterus is evacuated because a term-sized uterus prevented adequate exposure of the splenic fossa. In others, CS is necessary to prevent intrauterine death due to maternal hypoxia and/or hypotension.

Laparoscopic Splenectomy

Currently, there are two case reports of successful laparoscopic operation after blunt trauma causing a splenic rupture in 18- and 27-week pregnant women (one with diaphragmatic rupture and intrathoracic ruptured spleen) [52, 53]. Laparoscopic procedures are indicated in early presentations because in delayed presentation, blood clots obscure the operative field and there is a difficulty in visualization. Also in hemodynamically unstable patients, definitive treatment must be swift; therefore, laparotomy is recommended.

9.1.6.4 Endovascular Interventions

Splenic artery angiography followed by embolization in the general population has been described, with a reported success rate of 85% [54]. First, its role in the assessment and management of patients with hemoperitoneum is still unclear, and, second, if the pregnancy continues, there is a risk of ionizing radiation to the fetus.

9.1.6.5 Anesthetic and Perioperative Management

See Chap. 21.

9.1.6.6 Prevention and Treatment of Preterm Labor

See Chap. 23.

9.1.7 Prognosis

Due to the rarity of the condition, the maternal and fetal outcome for every etiology is difficult to estimate. Therefore, the outcome is mostly presented for the whole group of splenic ruptures.

9.1.7.1 Maternal Outcome

Maternal death is commonly due to massive hemorrhage and accompanying hemorrhagic shock and consumptive coagulopathy. In the conservatively treated group, the mortality rate was 100% [16]. Therefore maternal outcome depends on how fast has the splenectomy started from the onset of the rupture in massive hemor-

rhage. In 1952 Barnett stressed the severity of the condition with the maternal mortality of 54% [40]. Of all maternal deaths, 53% were recorded before 1880. Therefore, in the 1950s, maternal mortality was 35%. The importance of correct diagnosis and early operation is apparent when it is noted that of all the patients who were taken to the operating room for splenectomy, mortality was 19% [40]. The same percentage of overall maternal mortality was found in other studies from the same decade [5]. Also, in the 1950s the mortality from the spontaneous splenic rupture was 10% [29]. Up to 1967 reported overall maternal mortality was lowered to 8% in a series of 25 patients [6]. With 20 reported cases in the English literature between 1958 and 2011, maternal mortality rate in a spontaneous splenic rupture in pregnancy is 14.3% [32]. In two cases of emergent laparoscopic splenectomy, the mother has survived [52, 53].

9.1.7.2 Neonatal Outcome

Maternal hemodynamic decompensation leads to an acute decrease in uteroplacental perfusion, resulting in "fetal distress" and, ultimately, fetal demise [55]. Therefore, early diagnosis and intervention before hemorrhagic shock could lower fetal mortality rate. Specific information on infant survival is lacking. However, up to 1958, a fetal mortality was 59% [5]. Others claim fetal mortality of 70% for all types of the ruptured spleen [6, 40]. In the English literature between 1958 and 2011, the fetal mortality rate in a spontaneous splenic rupture in pregnancy was 42.9%; therefore, it is declining [32]. In two cases of emergent laparoscopic splenectomy, the fetus has survived [52, 53].

9.2 Ruptured Splenic Pregnancy

9.2.1 Definition and Classification

In about 20/1000 cases in pregnancy, the site of implantation is different from the uterine cavity (ectopic pregnancies): the most common site of ectopic implantation is the Fallopian tube (95.5%). Although rare (1.3% of ectopic pregnancies), an ovum could implant within the peritoneal cavity (abdominal pregnancies) either directly (primary abdominal pregnancies—extremely rare) or because of tubal rupture (secondary abdominal pregnancies). The criteria for *primary abdominal pregnancy* have been described by Studdiford in 1942 [56]:

- Normal Fallopian tubes and ovaries
- No evidence of uteroplacental fistula
- Pregnancy is related exclusively to the peritoneal surface and early enough to eliminate the possibility of secondary implantation after primary nidation of the Fallopian tubes

9.2.2 Incidence

There are 16 cases in the English literature of primary splenic pregnancies. The patients' mean age is highly variable (range 19–41 years) [57–59].

9.2.3 Pathophysiology

The liver and the spleen are more favorable for implantation because they are flat organs, rich in blood flow, and easily reached by the fertilized ovum (Fig. 9.5) [60]. However, both cannot allow placental attachment, thus leading to rupture with massive hemoperitoneum, if the pregnancy is left untreated (Fig. 9.6) [61].

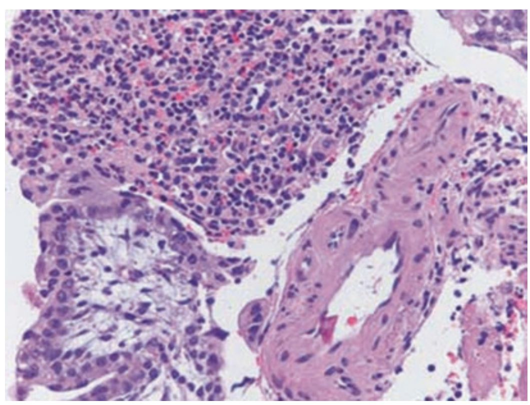


Fig. 9.5 Histopathological examination (20×): chorionic villi within the splenic tissue. Reproduced with permission from [57]

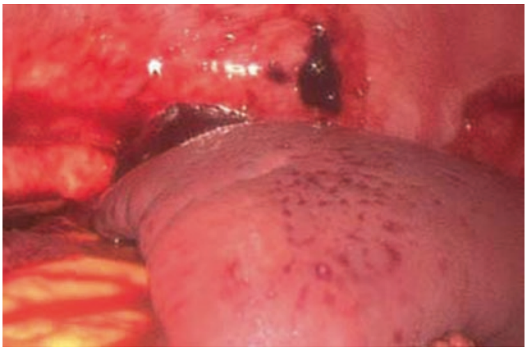


Fig. 9.6 Laparoscopic view, hemorrhagic lesion at the superior splenic pole. Reproduced with permission from [57]

9.2.4 Risk Factors

Risk factors related to abdominal pregnancies are similar to those of other ectopic pregnancies:

- Prior history of the pelvic inflammatory disease
- Prior ectopic gestation
- Endometriosis
- Reproductive assistance
- Uterotubal malformation
- Previous tubal surgery

9.2.5 Clinical Presentation

Most patients have prolonged amenorrhea but also in a period when the menstruation should occur. They present most commonly with sudden or short-lasting abdominal pain, radiating to the left shoulder (*Kehr's sign*). Depending on the severity of intraperitoneal bleeding, the pain can be localized or diffused. If the bleeding is massive, the patient can present with hemodynamic shock with pallor and cold sweat.

9.2.6 Diagnosis

In cases when pregnancy can be expected, βHCG should be checked. If elevated, transvaginal ultrasonography should be performed to define the uterine status and fetal status with a gestational sac. If normal-size uterus with a thickened endometrium without individual gestational sac is found, ectopic pregnancy should be suspected.

If Fallopian tube ectopic pregnancy is excluded, which is the most common, transabdominal ultrasound should be performed. Most of the gestations were subcapsular in location and assumed the appearance of an irregular mass that exceeds the contour of the spleen (Fig. 9.7). The appearance of an irregular mass outside the contour of abdominal viscus should raise the suspicion of ectopic abdominal pregnancy [62]. Nearly all patients with ruptured splenic pregnancy had a preoperative diagnosis of ruptured ectopic pregnancy.

In unequivocal cases without hemodynamic instability, abdominal CT is indicated (Fig. 9.8).

Fig. 9.7 Abdominal ultrasound showing the mass at the superior splenic pole (intraoperative view is seen in Fig. 9.6). Reproduced with permission from [57]

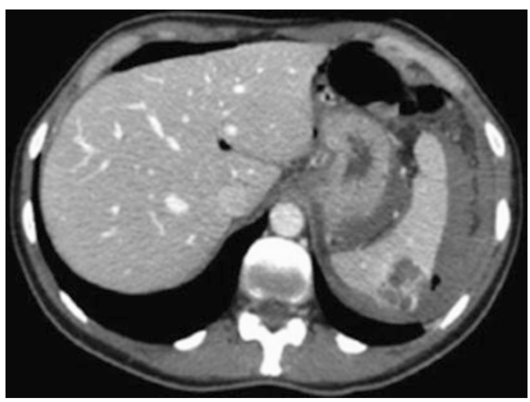


Fig. 9.8 Abdominal CT scan showing heterogeneous hypervascular mass at the superior splenic pole (intraoperative view is seen in Fig. 9.6). Reproduced with permission from [57]

9.2.7 Treatment

9.2.7.1 Surgical Treatment

It is difficult to make an accurate preoperative diagnosis, and, therefore, laparoscopy should be performed for diagnosis and possible treatment (Fig. 9.6). The entire abdominal cavity must be evaluated, and removal of ectopic pregnancy could be attempted, especially in the case of timely diagnosis. Successful emergency laparoscopic treatment of abdominal pregnancy associated with extensive hemoperitoneum has been reported in two cases [57, 62]. This shows that hemoperitoneum in abdominal pregnancy may be treated with laparoscopy and that conversion to laparotomy may not be necessary, at least in the case of splenic pregnancy, especially if the diagnosis is made early in the course of hemorrhage. Otherwise, median laparotomy should be made for visualization of all four abdominal quadrants and easier performance of the operation according to the underlying pathology.

9.2.7.2 Anesthetic and Perioperative Management

See Chap. 21.

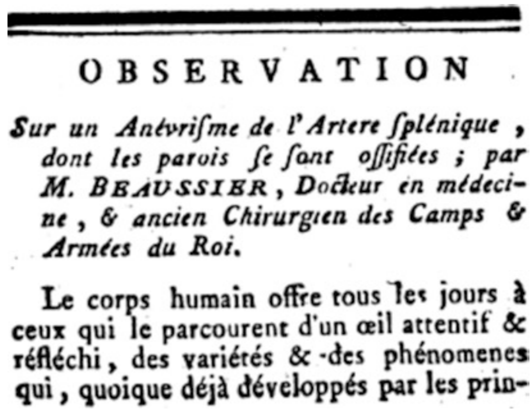
9.2.7.3 Prevention and Treatment of Preterm Labor

See Chap. 23.

9.3 Spontaneous Splenic Artery (Aneurysm) Rupture

9.3.1 Historical Perspective

Splenic artery aneurysm (SAA) is defined as an abnormal dilatation of the splenic artery more than 1 cm in diameter. The first case of SAA was published in 1770 by Beaussier [63] during the anatomic dissection of a 60-year-old female cadaver which he performed 10 years before publishing it (Fig. 9.9). This and the second case reported by Parker in 1844 [64, 65] were for many years omitted from the literature and priority mistakenly given to Crisp from 1847 by all subsequent authors, possibly because he himself


OBSERVATION

Sur un Anévriſme de l'Artere ſplénique, dont les parois ſe ſont oſſifiées ; par M. BEAUSSIER, Docteur en médecine, & ancien Chirurgien des Camps & Armées du Roi.

Le corps humain offre tous les jours à ceux qui le parcourent d'un œil attentif & réfléchi, des variétés & des phénomenes qui, quoique déjà développés par les prin-

Fig. 9.9 Original part of the text on the first case of SAA in the nonpregnant female by Beaussier. The text was published in 1770 in the *Journal de Medecine, Chirurgie, Pharmacie*. Reproduced with permission from [63]

had also erroneously credited Parker with the description of the first case [66]. Winkler, in 1903, was the first to identify SAA in a living person (a nurse) during laparotomy in a patient with abdominal pain of 8-year duration [67].

There is a strong association with pregnancy since Corson's first description of the sudden and unexpected death of a 29-year-old multigravida at 8 months' gestation in whom the diagnosis of rupture of an SAA was only made following postmortem examination in 1869 [68]. Sheehan and Falkiner in 1948 noted that 56% of females who suffered a rupture of an SAA were pregnant and in their last trimester [30].

9.3.2 Incidence

9.3.2.1 General Population

SAA is the most common (60%) of all visceral artery aneurysms. More than 50% of aneurysmatic ruptures in women under the age of 40 years are correlated to pregnancy, and the arteries most often involved are, in declining order, the aorta, cerebral arteries, splenic artery, renal artery, coronary arteries, and ovarian artery [69]. The incidence of SAA is unknown because a vast majority of SAAs (1) are smaller than 2 cm, (2) remain asymptomatic, (3) are generally encountered as autopsy findings [48], and [4] are due to destruction of spleen paren-

chyma and smaller vessels by hematoma, and some are classified as spontaneous spleen ruptures. Up to 1953, there were 204 recorded cases of both ruptured and unruptured SAA [70, 71]. The incidence of SAA in reports of autopsy series ranges 0.01–10.4% [72–74]. It is likely that the figures quoted in most autopsy series represent underestimates as the aneurysms can be difficult to identify unless their presence is specifically sought. SAAs are being detected incidentally in the course of sophisticated imaging for unrelated conditions. The majority of SAAs are <3 cm in diameter and are usually saccular, isolated, and located in the mid or distal portion of the splenic artery, frequently at an arterial bifurcation [75–77]. Macroscopically, there are two principal types of SAAs: saccular and fusiform (Figs. 9.10 and 9.11).

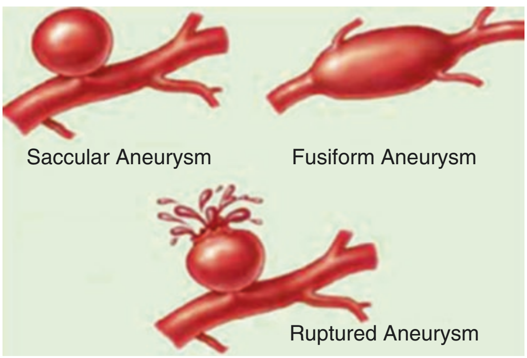


Fig. 9.10 Types of splenic artery aneurysm. Reproduced with permission from [78]

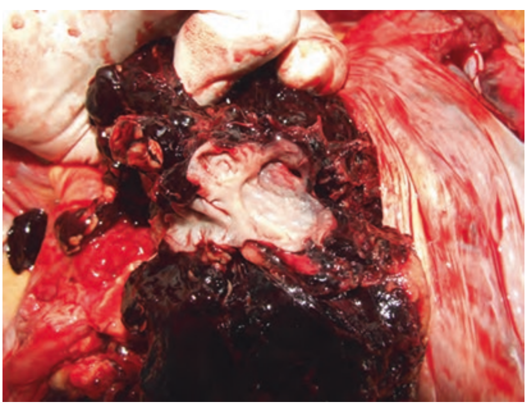


Fig. 9.11 Ruptured saccular aneurysm (2.5 cm in diameter) of the splenic artery found on autopsy of pregnant woman. Reproduced with permission from [79]

9.3.2.2 Splenic Artery Aneurysm Rupture

The principal complication of an SAA is a rupture, and the reported risk varies 3–9.6% [76, 80]. Nevertheless, to date, more than 400 cases of ruptured SAAs in the general population have been reported in the literature, with approximately 20–50% of these during pregnancy [48, 76, 80–88]. A summary of 58 recorded cases was made by Anderson and Gray in 1929, adding their own case [89], and Machemer and Fuge in 1939 collected a further 24 cases and added one of their own [90]. Sherlock and Learmonth in 1942 [91] stated that SAA sometimes declares itself during pregnancy and this may partly account for the larger number of females in the general population. This incidence is particularly interesting as aneurysms at all other common sites are undoubtedly more frequent in males [92]. SAAs are the most frequent in the general population with an incidence around 60%. Among visceral aneurysms, the SAA is the most common (95%) in young pregnant women, and a greater number of diagnoses are made during pregnancy, often due to aneurysmal rupture. Of all SAAs, 65% are present in pregnant women, and 50% rupture during pregnancy [93]. Grand multiparous form about 40% of women with SAAs [94]. In Owens and Coffey's series, 24% of the women were pregnant. When only the group in the childbearing age is considered, the incidence of SAA rises to 53% [71].

9.3.2.3 Trimester Distribution

A significant percentage of women are pregnant when the diagnosis is made probably due to augmented use of ultrasonography and high-resolution cross-sectional imaging techniques [77]. Sheehan and Falkiner in 1948 noted that 56% of females who suffered a rupture of an SAA was pregnant and in their last trimester [30]. The incidence of rupture of the SAA during pregnancy is as follows [76, 78, 95–98]:

- First to second trimester: 12%
- Third trimester: 69%
- Childbirth: 13%
- Puerperium: 6%

9.3.3 Risk Factors

There are two distinct types of splenic artery rupture: one is spontaneous splenic rupture where no underlying pathology of the splenic artery could be found and another is spontaneous rupture of the SAA. True SAAs (in general population) are commonly associated with a number of conditions, such as pregnancy and portal hypertension being the most common [73, 99–102]; other conditions include essential hypertension, angiodysplasia, atherosclerosis, diabetes, intracranial aneurysm, polyarteritis nodosa, alpha-1 antitrypsin deficiency, and infective factors [88, 100, 103, 104].

Data suggest rupture rates in general population of 2–3% [98, 105]. The size of the SAA is usually more than 2.5 cm in most patients at the time of rupture [80]; however, rupture of smaller aneurysms has also been reported [80, 96, 98].

9.3.3.1 Spontaneous Splenic Artery/Vein Rupture

Cases of spontaneous rupture of the normal splenic artery (or vein) had risk factors of long-standing cirrhosis of the liver with portal hypertension [106]. Prolonged hypertension may be a contributory factor [107, 108].

9.3.3.2 Spontaneous Splenic Artery Aneurysm Rupture

Almost all cases of ruptured SAAs in pregnancy have occurred during the third trimester [88]. Therefore, it is evident that the physical history of pregnancy gradually increases the risk of rupture of SAA. Apart from the late stage of pregnancy, other risk factors include portal hypertension [45, 109, 110], atherosclerosis, congenital abnormalities of the vessels, inherited vascular and connective tissue disorders (medial fibrodysplasia), vascular trauma, inflammatory processes, and degenerative arterial disease [35, 73, 76]. Although the average parity of women at rupture is 4.5 [77, 88, 98, 100, 105], there are cases with nulliparous women [102, 109, 111]. High blood pressure, common in preeclampsia-eclampsia, is a precipitating factor for SAA rupture, especially during labor [112].

9.3.4 Pathophysiology

The mechanisms involved in the formation of this vascular defect still remain unclear. Most theories consider hemodynamic and hormonal alterations in the late stages of pregnancy [113]. Although the risk of rupture mainly exists in the third trimester of pregnancy (see Sect. 9.3.3.2), there are cases of SAA rupture during the first trimester of pregnancy [114–117]. Only 5% are found during puerperium [82].

One of the mechanisms promoting the vascular defect in splenic arteries during the late stages of pregnancy seems to be the escalating increase of the circulating estrogens and progesterone during pregnancy [100]. The elevation of the levels of these hormones has been associated with the promotion of various structural alterations in the arteries, such as the disruption of the internal elastic lamina, fragmentation of elastic fibers, degeneration of smooth muscle fibers, and failure of elastin formation [118]. Additionally, it appears that the elevated levels of relaxin throughout the third trimester of pregnancy may affect the elasticity of the splenic artery wall [119] and could probably weaken the arterial wall [77, 95, 120]. Especially in the case of multiparity, the repeated exposure to these hormonal shifting could explain the increased incidence of rupture of SAA in this group of pregnant women.

It is also assumed that hemodynamic changes which occur during the late stages of pregnancy are implicated in the etiology of SAA ruptures during this period. More specifically, due to the fact that the increased size of the uterus tends to compress the aorta and the iliac arteries, resulting in higher flow in the splenic artery, the development of the SAA is enhanced; moreover, the increases in blood volume and cardiac output, along with the relative portal congestion, contribute to the formation of SAAs [113]. Also, compression of other surrounding pathologic conditions can contribute to faster development and progression of SAA or cause rupture of the normal splenic artery [81]. The vessel wall is in a continual state of self-maintenance and self-regulation including remodeling that occurs in response to hemodynamic stress [83]. It is sug-

gested that remodeling of the vessel wall causes similar histological lesions, regardless of the pathogenic factors [121].

9.3.5 Clinical Presentation

Apart from asymptomatic SAA found incidentally during pregnancy, there are two types of presentations depending if the SAA is only symptomatic or there is a true rupture.

9.3.5.1 Ruptured Splenic Artery (Aneurysm)

This rupture can be either sudden rupture or a two-stage rupture, which is present in 20–25% of cases [96–98]. In terms of clinical manifestations, the rupture of SAA is undoubtedly presented as an acute abdomen. In the early stages of rupture, diffuse tenderness in the upper abdomen, in the left hypochondrium, or over the uterine fundus may be elicited, accompanied by vomiting and in severe cases derangement of the vital signs, compatible with developing hemodynamic shock. The physical course either can consist of one stage, leading to dramatic collapse as a result of inability of self-containment of bleeding, or can present in a two-stage sequence, first described by Bockerman in 1930, when initial tamponade of hemorrhage in the lesser sack was made by clots blocking the foramen of Winslow [119, 122]. In these patients, initial hemorrhage into the lesser sac may cause pain and transient hypotension; the gradual increase of pressure in the lesser sac would be suddenly followed by a rupture into the greater sac and lead to massive intraperitoneal bleeding and shock, causing the patient to collapse. The initial phase where hemorrhage remains confined to the lesser sac provides vital time for diagnosis and preparation for intervention [77, 95, 96, 120]. The "sentinel" period between the initial and subsequent hemorrhages may take 6–96 h. This phenomenon of "double rupture" is found in 25% of reported cases [72, 102]. When ruptured, it usually causes acute left-sided abdominal pain that may radiate to the back, flank, and subscapular region and may cause shock, abdominal distention, and death. Due to diaphragmatic irritation with blood, in addition to abdominal pain, patients can also present with chest pain and dyspnea [107].

In the series reported by Owens and Coffey, ruptures in the general population were distributed as follows: 38% into the peritoneal cavity, 10% into the stomach, 7% into the colon, 4% into the pancreas, and 2% into the splenic vein [71].

9.3.5.2 Symptomatic Splenic Artery Aneurysm

The symptoms of an unruptured aneurysm are variable and may be completely lacking. According to Pasternack and Shaw [123], the pain of a colicky nature in the left epigastrium or hypochondrium may occur and is characteristically increased by exertion or by changes of posture. There may also be symptoms referable to the stomach, gallbladder, or colon. A periumbilical pulsating mass may be felt or a systolic bruit heard. There are no physical signs that reliably indicate the presence of an SAA [77].

9.3.6 Differential Diagnosis

Ectopic pregnancy is one of the first differential diagnoses for cases presented during the first trimester of pregnancy [114–117]. Approximately 70% of cases are diagnosed initially as a uterine rupture [69]. Differential diagnosis of pancreatic cysts or pseudocysts should be made, by location; this condition is more frequent in patients with past history of pancreatitis. Presentation similar to massive pulmonary embolism characterized by left-sided chest pain, breathlessness, and low oxygen saturation has been reported [124].

9.3.7 Diagnosis

The key to effective management of a ruptured SAA is increased clinical suspicion, combined with the accurate implementation of the diagnostic imaging, particularly abdominal sonography and angiography if permitted by the hemodynamic stability.

A diagnosis of ruptured SAA should be considered in (1) a pregnant woman who complains of the sudden onset of severe left upper abdominal pain regardless of whether pain or shock is prominent at the time of evaluation and (2) when a hemorrhagic shock in a pregnant woman without obstetric hemorrhage is present [109, 125].

Högler, in 1920, made the first preoperative diagnosis on the basis of bruit and a pulsatile mass on fluoroscopy [126]. Another case of one of the first preoperative diagnoses in the general population based on roentgen examination alone was made by Lindboe in 1932 [127]. In 1950, Evans obtained the first translumbar aortogram demonstrating an SAA which was operated successfully. Baum in 1965 used selective angiography in making a preoperative diagnosis.

Screening of the splenic artery by transabdominal ultrasound and Doppler should be considered selectively in pregnant patients with predisposing factors like hypertension, multiparity, and liver and pancreatic diseases (Fig. 9.12). However, its utility is limited by operator dependency, obese patients, bowel gas shadow, and arteriosclerosis [128]. Gray-scale sonography is not a useful diagnostic tool for SAA. Clinicians should use color Doppler sonography in the evaluation of the splenic hilum [128]. The likelihood of missing smaller lesions is also quite high because of limited spatial resolution [129].

Fig. 9.12 Abdominal sonography of ruptured splenic artery aneurysm showing clots around. Reproduced with permission from [78]

Although it is not the first-line investigative tool for SAA, plain abdominal X-ray carried out for some other abdominal pathology may reveal calcified SAA as a characteristic calcified ring with a central lucent area to the left of the first lumbar vertebral body [113].

Contrast-enhanced (i.v.) abdominal CT can reveal abdominal aorta with its branches. A splenic artery with SAA can be delineated (Fig. 9.13). The CT should be carefully analyzed because there are cases with more than one SAA [84, 130]. 3D reconstruction is important to precisely define the location, the diameter of the SAA which is important for preoperative planning (Fig. 9.14).

Fig. 9.13 Abdominal MSCT angiography showing splenic artery aneurysm arising from the mid-splenic artery and another smaller aneurysm at the proximal splenic artery. Perisplenic and retroperitoneal hematoma was evacuated during the operation the previous day. Reproduced from [84] under the CC BY 3.0

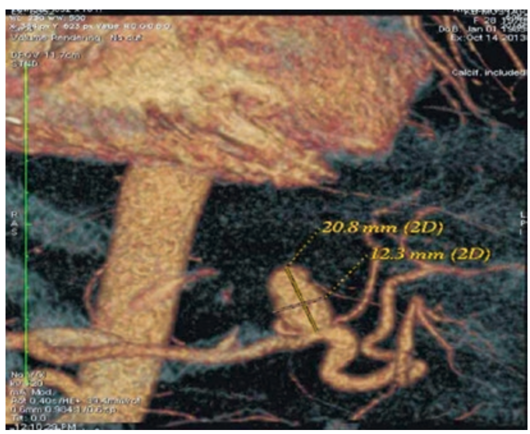


Fig. 9.14 Abdominal MSCT angiography with 3D reconstruction verifies the exact position of saccular splenic artery aneurysm measuring 20.8 × 12.3 mm. Reproduced with permission from [131]

Magnetic resonance angiography of the abdominal aorta and branches is performed in general population. MR angiography accurately defines the abdominal aorta with its branches, and it can accurately define SAA. There are no cases with MR-proven SAA in pregnancy.

9.3.8 Treatment

9.3.8.1 Ruptured SAA

Concerning intervention options, apart from the need of initial aggressive resuscitation, embolization of the SAA or emergency surgery is the mainstay of treatment options [113, 119].

The first successfully treated case in pregnancy was described in 1940. The management of ruptured SAA requires awareness and aggressive surgical approach. Aneurysmectomy with splenectomy, distal pancreatectomy with splenectomy with ligation of the proximal and distal splenic artery, and aneurysmectomy alone with splenic conservation are the procedures described [69, 95].

Splenic conservation is desirable but is difficult in the emergency setting with ruptured SAA [46, 95]. Angiography and embolization have been described for pseudoaneurysms and for unruptured true aneurysms [95]. In the high-risk patients, arterial embolization using coils can be an effective early treatment [69, 77, 120]. There are cases when emergency CS is performed with preoperative suspicion of placental abruption or uterine rupture. If the general or abdominal surgeon is not available, some of these patients are sent to abdominal CT scan with i.v. contrast postoperatively [84] due to [1] continuous bleeding and [2] no fear of ionizing radiation to the fetus [84]. This is not a recommended diagnostic and treatment algorithm. The bleeding should be stopped during the initial operation.

9.3.8.2 Symptomatic SAA

The management of a unruptured aneurysm is more controversial, although elective resection of those found in pregnant women and women of childbearing age is recommended if the SAAs are larger than 2 cm [73, 88, 98]. Surgical treatment options include resection of an aneurysm, with or without splenectomy, via laparotomy or laparoscopy. Aneurysms located in the proximal or middle third of the splenic artery may be treated with simple excision, with proximal and distal ligation of the artery and splenic preservation (vascularized through the short gastric vessels). For aneurysms located in the distal third, resection with splenectomy is most often performed, which is, unfortunately, the case in 70% of the patients with portal hypertension [105, 132].

Endovascular radiological techniques that have been employed in the general population include transcatheter embolization and percutaneous angiographic embolization [133] and could be used in the puerperium. *Postembolization syndrome* and infarcts are common events (30%) but generally resolve without a sequel. The gestational age is an important parameter for the indication of this technique in pregnancy.

9.3.8.3 Anesthetic and Perioperative Management

See Chap. 21.

9.3.8.4 Prevention and Treatment of Preterm Labor

See Chap. 23.

9.3.9 Prognosis

Ruptured SAA treated up to the 1940s, and during the 1950s, resulted in equal maternal mortality of 93.3% [134, 135]. Early consideration and diagnosis of ruptured SAA significantly increase the chances of survival for both the mother and the fetus. In Australia, in 30 years (1967–1999), there have been only four maternal deaths due to SAA rupture [135]. By way of comparison, in the UK for the period 1988–2002, there were seven definite (and one possible) cases of a ruptured SAA [73]. But in a 10-year review of maternal mortality in Singapore, not a single case of SAA was identified [136]. Review from North America confirms the rare incidence and therefore rare mortality from this entity [137].

In the general population, there are some 400 reports with an overall mortality rate of 25% [73]. Approximately 25% involve pregnant women, and in this group, the mortality is disproportionately higher at 75% for mothers and a fetal mortality rate approaching 95% [45, 73, 102, 124, 138]. The literature now contains more than 100 cases of ruptured SAAs in pregnancy but only 16 cases with both maternal and fetal survival [73, 122, 139], underlining the necessity of immediate intervention. Pregnant women tend to be younger and have fewer adhesions from previous surgery than the general population; therefore, rupture occurs almost exclusively into the free peritoneal cavity [73, 100, 140]. In early pregnancy when clinicians do not expect rupture of SAA, maternal mortality is high due to cardiac arrest during the early postoperative period [114, 115].

9.4 Spontaneous Splenic Vein (Aneurysm) Rupture

9.4.1 Historical Perspective and Incidence

Portal system aneurysms can be divided into two types: extrahepatic and intrahepatic. Splenic vein aneurysm (SVA) is a true aneurysm and belongs to the extrahepatic category. In 1953 Lowenthal and Jacob [141] described the first case of SVA in general population, and there are ten pregnant women with splenic vein rupture described [108, 142–150]. Splenic vein rupture in a pregnant woman was first described in 1959 by Rahn and Steffen [144]. Up to 1961, there were only two references of the *spontaneous* splenic vein rupture in general population [106, 151] and also two cases of spontaneous rupture in pregnancy [107, 108]. Splenic vein rupture usually occurs during the third trimester, whereas splenic artery rupture has been described at any time from the first trimester through to the puerperium. There is only one case of SVA rupture occurring immediately postpartum [142]. Despite the difference in incidence, SAA and SVA share a number of etiological factors, presenting symptoms, clinical course, complications, and management.

9.4.2 Etiology

The origins of the ruptures due to vascular pathologies at pregnancy may be hormonal, genetic, thrombotic, or mechanical. The etiology of splenic aneurysms is speculative and may include congenital causes such as local failure of connective and elastic tissue [146, 147]. Aneurysms may also be acquired due to trauma, inflammation, or portal hypertension [148, 150] or cirrhosis [106, 151].

Splenic aneurysms are more common in multiparous women; it is, therefore, possible that pregnancy may influence their development because of changes in hemodynamic and increased levels of progesterone [105]. The physiological increase in blood volume and cardiac output during pregnancy could lead to portal congestion and splenic arteriovenous shunting and, together with progesterone-induced vasodilatation and vessel wall weakness, could favor aneurysm formation. Tolgonay et al. [152] described a case of splenic size increase and SVA due to a systemic infection in a patient with leukemia. After appropriate therapy, a reduction in spleen size was observed followed by a decrease in splenic vein blood flow and a regression of the SVA. Recent studies have shown an alteration of elastic fibers in the internal elastic lamina and fibrodysplasia of the media lamina as the consequence of hormonal changes. These factors may become cumulative, explaining the increase of rupture of the splenic vessels as parity rises [69]. The etiology of SVA in nonpregnant women includes portal hypertension and liver cirrhosis [153], chronic pancreatic inflammation [154], and vessel wall weakness [155]. Splenic vein rupture during pregnancy is associated with acute pancreatic necrosis eroding the splenic vein, acute vessel wall inflammation [108], and SAA rupture into the splenic vein [156]. In other cases, the etiology remains unknown, and splenic vein rupture is labeled “spontaneous” to account for the lack of apparent trauma or disease.

9.4.3 Risk Factors

There are only two cases of pregnant patients with spontaneous rupture of the normal splenic vein. Gross and microscopic examination of the spleen revealed splenomegaly with the spleen measuring 11.5 × 8.5 × 7 cm and weighing 252 g (Fig. 9.15). No specific pathologic lesion was seen grossly or microscopically in the spleen. There was a perforation of one of the branches of the splenic vein at the hilum of the spleen without underlying pathology. Prolonged hypertension may be a contributory factor [107, 108].

9.4.4 Pathophysiology

9.4.4.1 Cirrhosis

The SVA was associated with portal hypertension and liver cirrhosis in 50% of nonpregnant patients. The pathogenetic mechanism of splenic vein rupture could be supported by three clinical observations:

1. Splenomegaly in cirrhosis is not only caused by portal congestion, but it is mainly due to tissue hyperplasia and fibrosis. The increase in spleen size is followed by an increase in splenic blood flow, which participates in portal hypertension actively congesting the portal system [157].

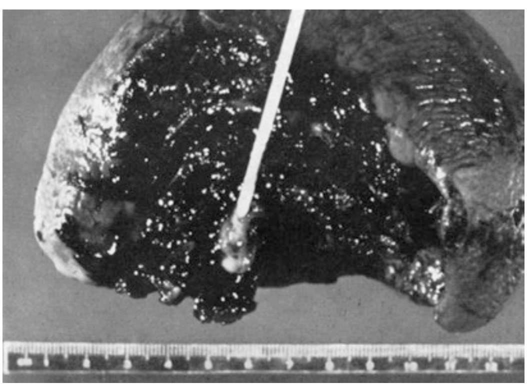


Fig. 9.15 Hilar surface of the spleen showing hemorrhage about splenic vessels. Probe inserted into spontaneous perforation of splenic vein. Reproduced with permission from [108]

2. Increased resistance to portal blood flow is the primary factor in the pathophysiology of portal hypertension and is mainly determined by the morphological changes occurring in chronic liver diseases. The transmission of the increased blood flow and pressure to the splenic vein may lead to progressive dilation and weakness of the vein wall.
3. Portal hypertension in advanced cirrhosis is characterized by an increase in vasoactive mediators such as prostaglandins, nitric oxide, serotonin, and hormonal derangements, which may cause structural and functional changes in the splenoportal venous system [157].
4. The reduction in the size of an aneurysm is related to a decrease in splenic vein blood flow [152]. These observations suggest that the persistent stagnation of blood flow in the portal system may play a major role in the development of the SVA.

9.4.4.2 Hemodynamic and Hormonal Changes in Pregnancy

An increase in cardiac output and blood volume, usually found in the later months of pregnancy, is an important factor in the precipitation of vascular accidents [69]. An increase in estrogen receptor expression in endothelial and vascular smooth muscle layers of arteries is associated with increased relaxation via endothelium-derived vasodilators and inhibition of Ca^{2+} entry into the vascular smooth muscle [158]. The increase in blood volume, the hypertrophy, or the dilation of the veins and changes in venous pressure related to pregnancy seem to be involved in the pathogenetic mechanism [146]. Hemodynamic and hormonal changes may be the cause of vascular alterations, which can lead to a weakening of the vein wall (Fig. 9.16).

9.4.4.3 Mechanical Factors

Lax perisplenic ligaments can lead to splenic torsion which can result in splenic vein rupture (see Sect. 9.5).

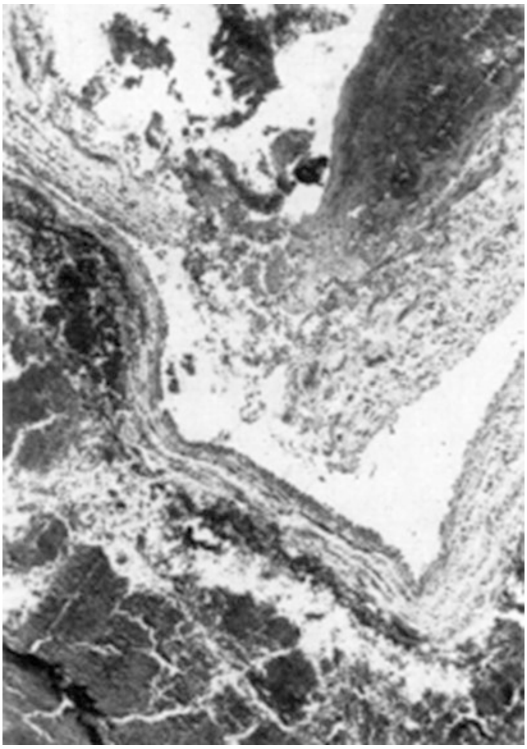


Fig. 9.16 Photomicrograph of splenic vein showing an acute inflammatory reaction and fibrinoid alteration in the vein wall with perforation and surrounding hemorrhage. Reproduced with permission from [108]

9.4.5 Clinical Presentation

Abdominal venous aneurysms including SVA are usually incidental findings. However, 75% of non-pregnant patients had clinical complaints: 50% had abdominal pain, and all had abdominal fullness and hepatic dysfunction. One patient presented in a state of shock with intra-abdominal bleeding. The similarity between spontaneous perforation of the splenic vein and SAA rupture is striking in many aspects: symptoms, signs, and the lucid interval of amelioration of symptoms, occurrence in late pregnancy, and the therapeutic indications in both conditions [106, 108, 159–161].

Depending on the mechanism, extent, and location of the splenic vein rupture, the severity of the bleeding can be variable. If significantly severe, upper abdominal pain and nausea are followed by collapse. The patient recovers after several minutes, but the abdominal pain continues. The pain can be present on the top of the left (*Kehr's sign*) or both shoulders [108]. If the hemorrhage is slower or the patient is referred to the hospital early, there is no collapse in the course of the disease.

9.4.6 Differential Diagnosis

Differential diagnosis is the same as for the SAA (see Sect. 9.3.6).

9.4.7 Diagnosis

In general population, angiography is the imaging of choice for diagnosing the visceral aneurysm (rupture) if the patient is hemodynamically stable. In selected cases, it is also a treatment modality. Abdominal CT scan with i.v. contrast (arterial and venous phase) can reveal the correct diagnosis in a hemodynamically stable patient. In certain cases, the diagnosis is made intraoperatively or unfortunately during autopsy (Fig. 9.17) [79, 145].

9.4.8 Treatment

9.4.8.1 Surgical Treatment

The natural course of unruptured SVA is uncertain; therefore, when patients in the general pop-

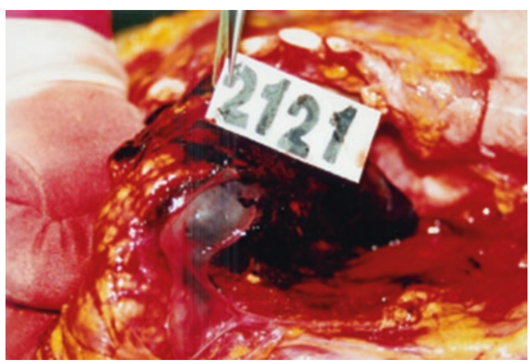


Fig. 9.17 Hematoma and spontaneous rupture at the splenic vein 3 cm from the splenic hilum on autopsy in the fifth month of pregnancy. Reproduced with permission from [145]

ulation are asymptomatic, treatment is controversial. In order to avoid the risk of rupture, it has been suggested that for 1–2 cm lesions, patients should be followed up on a regular basis with abdominal CT, abdominal MRI, or transabdominal color Doppler ultrasound. If inflammation is present as in accompanying chronic pancreatitis, every SVA should be treated surgically because rupture is possible despite aneurysm diameter [154]. However, the most secure recommendation is that in pregnancy, even the smallest SVA should be treated surgically [142].

Because of the already damaged vein wall, repair of the vein should be avoided. Control of the bleeding, ligation of the vein, meticulous hemostasis, and splenectomy are the appropriate treatments. Splenectomy has long been advocated to correct the pancytopenias which result from the hypersplenism, associated with portal hypertension in cirrhotic patients. However, even though this intervention may correct the hematological picture, it should be noted that it rarely changes the course of the underlying disease. The standard management of SVA rupture remains emergency surgery which allows SVA resection, distal pancreatectomy, splenectomy, and splenorenal shunt [155].

9.4.8.2 Anesthetic and Perioperative Management

See Chap. 21.

9.4.8.3 Prevention and Treatment of Preterm Labor

See Chap. 23.

9.4.9 Prognosis

9.4.9.1 Maternal Outcome

It is difficult to discuss the prognosis due to several patients with splenic vein rupture during pregnancy. Probably due to slower bleeding then with rupture of SAA, the prognosis is expected to be better. Maternal mortality is almost nil, and all survived except the mothers that died due to exsanguination before the operation [108, 142, 143, 145, 146].

9.4.9.2 Fetal Outcome

Despite excellent maternal survival, fetal survival is poor. This is due to exsanguination which results in fetal distress and intrauterine fetal death. Only fetal survival recorded is in patients that presented postpartum [108, 142, 143, 145, 146].

9.5 Splenic Torsion

9.5.1 Historical Perspective and Incidence

Splenic torsion is an exceedingly rare complication in pregnancy. The first case of successful splenectomy due to the splenic torsion in pregnancy was made by Meek in 1907 [162]. There are only several cases published during pregnancy and puerperium [162–165].

9.5.2 Etiopathogenesis

It is a complication of the wandering spleen, a rare condition characterized by increased splenic mobility due to the absence or laxity of its suspensory ligaments that may present as acute abdomen when it is twisted on its pedicle [166]. It has been reported in conditions such as abdominal trauma, splenomegaly, nonspecific abdominal muscle laxity, and laxity resulting from the hormonal effects of pregnancy [167]. It has been suggested that the softening effect of pregnancy hormones on ligaments, the abdominal musculature, diminished peritoneal cavity volume as a result of the gravid uterus, and a maximal third-trimester increase in whole-blood volume might be the predisposing factors in pregnancy [163, 164].

9.5.3 Clinical Presentation

Symptoms of splenic torsion vary depending on the degree of torsion. Mild torsion might manifest with chronic abdominal pain resulting from congestion; moderate torsion might manifest with severe intermittent abdominal pain related to intermittent rotation and derotation [16, 162, 163]. Severe and acute torsion present with

symptoms suggestive of an intra-abdominal catastrophe [164, 167]. Intermittent moderate abdominal pain is sometimes attributed to other diseases [162], such as acute pancreatitis [168].

9.5.4 Differential Diagnosis

The most common preoperative differential diagnosis is splenic infarction, symptomatic/ruptured SAA, or SVA.

9.5.5 Diagnosis

Preoperative diagnosis is difficult, and definitive diagnosis is commonly encountered during surgical exploration.

9.5.6 Treatment

9.5.6.1 Surgical Treatment

Treatment is always surgical. Initial exploration by laparoscopy or laparotomy depends on surgeon's preference. The further surgical procedure depends on the status of the spleen. If longstanding detorsion is present with infarction and gangrene of the spleen, splenectomy is indicated (Fig. 9.18). If exploration is done early when the spleen is still vital, detorsion with splenopexy is indicated (Fig. 9.19).

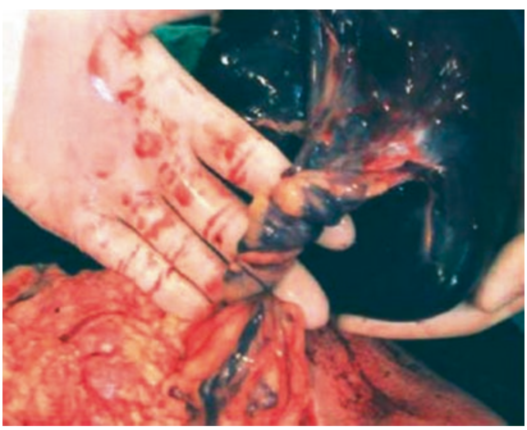


Fig. 9.18 Torted vascular pedicle of wandering spleen with infarcted, hypermobile spleen. Reproduced from [164] under the CC Attribution License

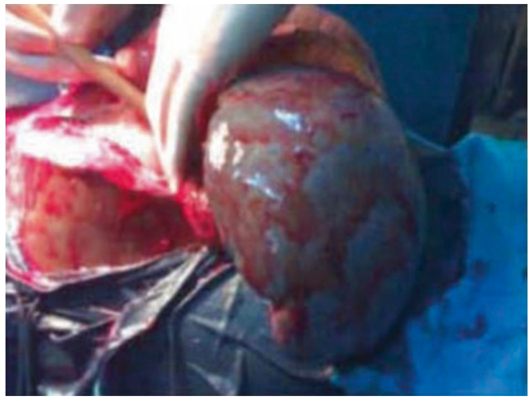


Fig. 9.19 Enlarged and vital spleen on its twisted pedicle. Reproduced with permission from [169]

9.5.6.2 Prevention of Future Torsion

If the torsion is intermittent and there is an underlying pathology (such as autoimmune thrombocytopenic purpura) predisposing to torsion, then splenectomy is performed. If there is no underlying pathology, then splenopexy is performed. The best timing is either before pregnancy or if symptoms persist during pregnancy then the second trimester. The second trimester carries the lowest risk of obstetric complications. With modern imaging techniques, the risk of future torsion (due to enlarged or ectopic spleen) can be adequately estimated before and during pregnancy. Another indication for splenectomy is external compression of the ureter (with or without hydronephrosis). MRI and MR angiography are sensitive and noninvasive techniques providing a stereoscopic evaluation of the hilar vessels of the spleen in order to make a safe prediction of the risk for torsion [170].

9.5.6.3 Anesthetic and Perioperative Management

See Chap. 21.

9.5.6.4 Prevention and Treatment of Preterm Labor

See Chap. 23.

9.5.7 Prognosis

Prognosis depends on the severity and duration of splenic torsion. If operated early in the course of the diseases, prognosis is excellent. If the mother presents with hemorrhagic shock, fetal mortality is likely [169].

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10 Abdominal Trauma

Abstract

Abdominal trauma is one of the most complex scenarios in emergency abdominal surgery during pregnancy. General classification on blunt and penetrating trauma helps in the diagnostic pathway and therapeutic management. Penetrating trauma most commonly includes growing uterus and the fetus which act as a shield for maternal intra-abdominal organs. In such cases, especially stab wounds, the maternal outcome is excellent. The fetal outcome depends on the underlying fetal, amniotic, and uterine injuries. Significant injury to abdominal organs after blunt trauma is more difficult to diagnose and treat. All maternal abdominal organs could be injured, and injuries are sometimes difficult to diagnose early, especially when clinicians are reluctant to use abdominal CT during pregnancy. Blunt abdominal trauma carries a risk of injury to both reproductive organs (uterine rupture, placental abruption) and digestive tract (hepatic or splenic rupture, intestinal perforation). Therefore, interdisciplinary approach which includes an abdominal surgeon and a gynecologist during diagnostic workup, as well as therapeutic management, is critical to optimize maternal and fetal outcome.

10.1 General Considerations

10.1.1 Incidence

Injuries resulting in an emergency department visit occur in 3–7% of pregnancies [1–3]. A reported 0.3–0.4% of pregnant women require hospital admission because of trauma [1, 2, 4, 5]. Motor vehicle accidents (MVAs) are the leading cause of maternal injury, comprising up to 80% of trauma in pregnancy [3, 6–8]. The overall incidence rate of MVAs during pregnancy has been estimated at around 207/100,000 pregnancies [9]. In the United States, the annual crash rate for pregnant women has been estimated as at least 13/1000 person-years as compared with 26/1000 person-years among nonpregnant women [10]. Pregnant patients represent 1.5–3.8% of all collision-related MVA [11, 12]. MVAs are responsible for about 50% of non-penetrating abdominal wounds and that the trauma is often severe and associated with other injuries [6, 13, 14]. Pregnant women involved in MVA are more likely to be in a motor vehicle rather than to be a bicyclist or pedestrian struck by a car as compared to nonpregnant women [11]. Approximately 6–7% of all pregnant women experience some sort of

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_10

physical trauma in the United States, and it accounts for 20% of maternal mortality [4, 13, 15–18]. By some, the falls are the most common trauma [19]. Significant trauma occurs to approximately 8% of pregnant women. Most trauma accidents (>50%) occur during the second and third trimester [6, 19]. In declining incidence, the etiology of maternal trauma is most often MVAs (55%), followed by falls (22%), assaults (22%), and burns (1%) [6, 13, 14, 20]. Estimated incidence/prevalence of injury by type of trauma during pregnancy is presented in the Table 10.1. Penetrating injuries constitute a greater proportion of injuries at inner-city centers [21, 22].

The pattern of serious injuries in pregnant women is different from that of nonpregnant trauma patients: injuries to the abdomen are more common than injuries to the head and chest. About 5% of fetal injuries occur without injury to the mother.

10.1.2 Risk Factors

10.1.2.1 Maternal Risk Factors

Major risk factors for maternal trauma include [11, 12, 24–28]:

- Young age (<25 years)
- African-American or Hispanic race
- Illicit drugs, alcohol, or smoking
- Domestic violence
- Noncompliance with proper seat belt use
- Epilepsy or other seizures
- Overweight and obesity
- Work outside the home
- Low socioeconomic status
- Medicaid insurance

When compared to nonpregnant trauma patients, pregnant women are younger and less severely injured [29]. Changed attitudes to pregnancy have resulted in women involving themselves increasingly in social, commercial, and professional activities virtually throughout their pregnancies, thus exposing themselves to a risk of accidental injury similar to that in the nonpregnant population. Pelvic ligamentous laxity and the protuberant abdomen of pregnancy contribute to the instability of gait, predisposing the pregnant woman to falls especially with the progression of pregnancy. The prominent abdomen, especially toward term, becomes vulnerable to any form of trauma, and it has been suggested that minor acci-

Table 10.1 Estimated incidence/prevalence of injury by type of trauma during pregnancy

Mechanism of injury	Estimated incidence/prevalence in pregnancy	Estimated incidence/prevalence outside of pregnancy
Motor vehicle crashes	207/100,000 live births	1104/100,000 women[a]
Falls and slips	48.9/100,000 live births	3029/100,000 women
Burns	0.17/100,000 person-years	2.6/100,000 person-years
Accidental poisoning	N/A	N/A
Domestic violence	8307/100,000 live births	5239/100,000 women[a]
Suicide[b]	2/100,000 live births	8.8/100,000 population[a]
Homicide	2.9/100,000 live births	2.3/100,000 women
Penetrating trauma[c]	3.27/100,000 live births[a]	3.4/100,000 women[a]
Toxic exposure	25.8/100,000 person-years	115.3/100,000 person-years

Literature relating to the incidence of burns during pregnancy is limited to most severe cases admitted to burn units and referral centers. The rate for accidental poisoning during pregnancy could not be calculated from available published literature. Domestic violence incidence includes all forms of partner violence: sexual, physical, and psychological. *N/A*, not available

[a]Rates calculated using 2009 US data from Centers for Disease Control and Prevention

[b]Rates exclude attempted suicides. *Attempted* suicide rate during pregnancy is approximately 40/100,000 pregnancies and during the postpartum period is 43.9/100,000 live births

[c]Rates include only causes leading to fatality

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dental injury is more common during pregnancy than at any other time in adult life.

The impact of mind-altering substances is significant. Data from the American College of Surgeons National Trauma Data Bank revealed that 19.6% and 12.9% of pregnancy-related traumas were associated with the use of illicit drugs or alcohol, respectively [12]. Intoxicant use is found in up to 45% of the pregnant population involved in MVAs [26]. Intoxication also contributes to a significantly lower use of restraints while driving when compared with sober patients (22% vs. 46%, respectively) [26]. These substances contribute to automobile accidents as well as low birth weights.

Mothers who reported an injury during pregnancy were more likely to be aged <18 years vs. 18–29 years and less likely to be aged ≥30 years. They were more likely to use alcohol during pregnancy, to smoke during pregnancy, to have epilepsy, and to be employed than mothers who did not report an injury [19]. The distribution by trimesters according to the intention and cause is presented in the Fig. 10.1. However, knowledge of characteristics specifically associated with injury among pregnant women can be used to help iden-

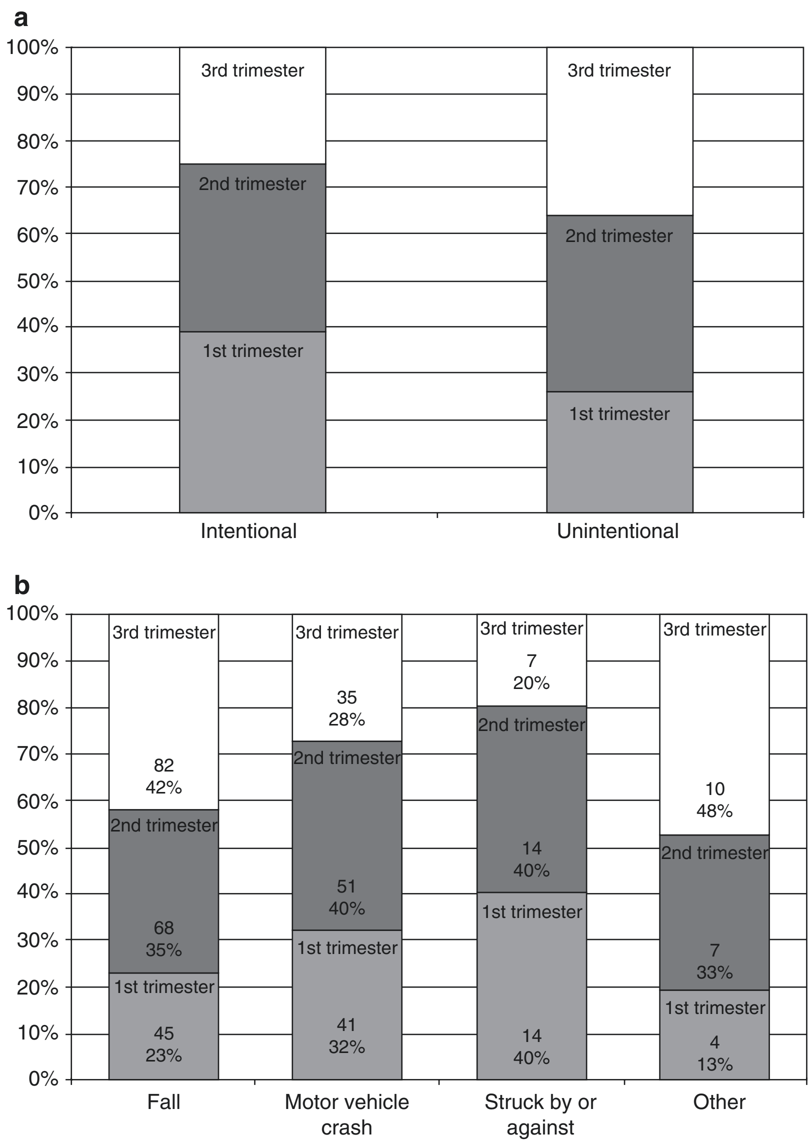

Fig. 10.1 Timing of injuries during pregnancy reported by mothers of control infants, (**a**) by intention, and (**b**) by cause. National Birth Defects Prevention Study, 1997–2005 [30] permission for the publication

tify women who may be at higher risk for experiencing an injury during pregnancy and can potentially inform the development of prevention programs for women to reduce the risk of injury during pregnancy. Many of these characteristics have been associated with adverse pregnancy outcomes, such as alcohol with fetal alcohol syndrome, smoking with orofacial defects and preterm delivery, and obesity with neural tube defects and Cesarean section (CS). Therefore, efforts to modify these exposures may have multiple positive impacts. For example, prevention of alcohol use during pregnancy could both reduce the fetus' direct risk from the alcohol exposure and reduce the risks of maternal injuries, which can also adversely affect pregnancy outcome. It is recommended that all pregnant women be screened for alcohol use at their first prenatal visit.

10.1.2.2 External Risk Factors

For instance, differences in these statewide motor vehicle crash rates during pregnancy may be a result of several country−/state-specific factors [31] and others:

- Birth rates
- Traffic/transportation law/regulations
- The severity of court sentence

10.1.3 Prevention

The primary way to protect the fetus is to protect the driver.

Lotta Jakobsson

Despite advances in trauma management, prevention is a key to increased maternal and fetal survival. MVAs and domestic violence are common preventable causes of trauma in pregnancy. MVAs are responsible for most severe maternal injuries and fetal losses from trauma [15, 32–35]. Pregnant women have low rates of seat belt use [4, 25, 33, 36]. Proper seat belt use is the most significant modifiable factor in decreasing maternal and fetal injury and mortality after MVAs [18, 37, 38]. Seat belt-restrained women who are in MVAs have the same fetal mortality rate as women who are not in MVAs, but unrestrained women in MVAs are 2.8 times more likely to lose their fetuses (see Sect. 10.2). Prenatal care must include three-point seat belt instructions (see Sect. 10.3.2.4) [12, 39–41]. Because many women are unaware of the potential for placental abruption without evidence of maternal injury, pregnant patients should be instructed to seek care immediately after any blunt trauma. Screening of younger patients is particularly important because they have higher rates of MVAs and domestic violence [42, 43]. Resource materials in waiting rooms and restrooms allow patients to gather information without confrontation [25].

10.1.4 Anatomic and Physiologic Changes Relevant to Trauma

10.1.4.1 Maternal Physiology

The possibility of pregnancy should be considered in all female trauma patients of reproductive age. Pregnancy causes anatomic and physiological changes involving nearly every organ system in the body, making the treatment of a pregnant trauma patient complex [44, 45]. Some of the anatomic and physiological changes in pregnancy that are relevant to trauma are presented in Table 10.2.

These changes, by altering the signs and symptoms of injury, may influence the interpretation of the physical examination as well as laboratory results of traumatized pregnant women. This may affect the approach and the response to resuscitation [44–46]. During the first trimester of pregnancy, the uterus is confined and protected by the bony pelvis (Fig. 10.2). It remains an intrapelvic organ until around the 12th week of gestation when it rises and becomes an abdominal one.

In the first two trimesters, the uterus is additionally protected by the amniotic fluid which acts as a hydraulic shock absorber, decreasing the force of the blow by transmitting it equally in all directions [48]. In the second trimester, the small fetus remains cushioned by a relatively large amount of amniotic fluid. Later in pregnancy, the fetal head is fixed in the pelvis, and the buffering

Table 10.2 Anatomic and physiological changes in pregnancy relevant to trauma

Organ system	Changes relevant to trauma
Uterus	*First trimester*: Intrapelvic organ protected by the bony pelvis *Second trimester*: Becomes an abdominal organ; the fetus is cushioned by a relatively large amount of amniotic fluid *Third trimester*: The uterus is large and thin walled
Blood	The increase in plasma volume greater than in RBC results in a decreased HCT
Cardiovascular system	The increase in plasma volume and a decrease in vascular resistance of the uterus and placenta cause an increase in cardiac output The increase in the cardiac rate *Second trimester*: Decrease in both systolic and diastolic blood pressure
Respiratory system	Increased tidal volume and minute ventilation Hypocapnia in late pregnancy Decreased residual volume
GI system	Gastric emptying time is prolonged *Third trimester*: The bowel is pushed upward and lies mostly in the upper abdomen
Other systems	Dilatation of the renal calyces, pelvis, and ureters The pituitary gland increases in size The symphysis pubis and the sacroiliac joints widen

RBC red blood cell, *HCT* hematocrit, *GI* gastrointestinal

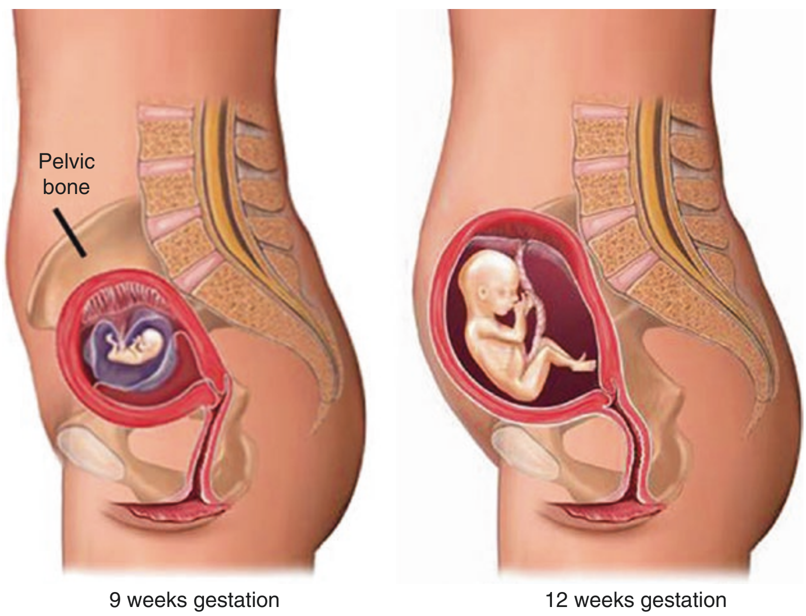

Fig. 10.2 The uterus is protected by the bony pelvis and remains an intrapelvic organ until the 12th week of gestation. Reproduced with permission from [47]

effect of the amniotic fluid is decreased, making the head prone to injury. By the third trimester, the uterus is large and thin walled [49]. The uterus and its contents have increased susceptibility to injury (penetration, rupture, placental abruption, and premature rupture of membranes). Some of the characteristics causing this increased susceptibility include the difference in elasticity between the uterus and placenta, which causes the uteroplacental interface to be subject to shear forces and may lead to placental abruption [50]. Plasma volume increases throughout pregnancy with plateau at about 34 weeks of gestation. A smaller increase in the number of red blood cells results in a decreased hematocrit [44, 49]. The placental vasculature is maximally dilated, yet it

is very sensitive to catecholamine stimulation [44, 49, 50]. An acute decrease in the intravascular volume may result in a significant increase in the uterine vascular resistance. This could cause a reduction in fetal oxygenation, even though the maternal vital signs can stay within normal range [15, 44, 46, 50, 51].

There are hemodynamic changes that are noted during pregnancy and that are relevant when dealing with injured pregnant patients. An increase in cardiac output is noted after 10 weeks of gestation that is due to the increase in plasma volume and the decrease in vascular resistance of the uterus and placenta. During the third trimester, the uterus and placenta receive 20% of cardiac output. A gradual increase in the cardiac rate, maximizing in the third trimester, must be considered when evaluating the tachycardiac response to hypovolemia. In the second trimester, there is a decrease in both systolic and diastolic blood pressure. Turning the patient to the left lateral decubitus position may, in some women, prevent hypotension [44, 49]. Increased levels of progesterone in pregnancy are thought to increase tidal volume and minute ventilation.

Hypocapnia is common in late pregnancy. The diaphragm elevates causing decreased residual volume. Maintaining adequate arterial oxygenation is important in the resuscitation of injured pregnant patients because of increased oxygen consumption during pregnancy [44]. The cardiovascular changes during pregnancy may complicate the evaluation of intravascular volume, the assessment of blood loss, and the diagnosis of hypovolemic shock [52]. Maternal hemodynamic measurements may not accurately reflect the status of the uteroplacental circulation. Animal studies have demonstrated that maternal heart rate and blood pressure may remain within normal ranges during a 20% acute blood loss or during a more gradual loss of 30–35% of estimated total blood volume [53]. Also, the unreliability of maternal blood pressure and pulse rate in predicting fetal loss is documented [54]. Pregnancy maximally dilates the uterine vasculature, so that autoregulation is absent and uterine blood flow is entirely dependent on maternal mean arterial blood pressure (MAP). Pregnancy represents a state of accelerated but compensated intravascular coagulation, which has both advantages and disadvantages for the pregnant trauma victim [52]. Increased levels of coagulation factors may improve hemostasis following trauma; however, at the same time, parturients remain at increased risk for thromboembolic complications during periods of immobilization. Because buffering capacity during pregnancy is diminished, pregnant trauma victims rapidly develop metabolic acidosis during periods or hypoperfusion and hypoxia.

Gastric emptying time is prolonged in pregnancy; therefore, in the emergency setting, early gastric tube decompression is important in order to avoid aspirations. In the third trimester, as the uterus enlarges, the bowel is pushed upward and lies mostly in the upper abdomen [49]. Therefore, in blunt trauma, the bowel is relatively protected, while the uterus and its contents (fetus, placenta) are more vulnerable. However, penetrating trauma to the upper abdomen can cause complex intestinal injury [44].

Other changes in pregnancy involving nearly every organ system in the body are important when treating a patient suffering a trauma. Physiological dilatation of the renal calyces, pelvis, and ureters is noted and should be taken into account when dealing with cases of pelvic and abdominal trauma. During pregnancy, the pituitary gland increases in size. Shock can cause necrosis of the anterior pituitary gland, resulting in pituitary insufficiency. The symphysis pubis and the sacroiliac joints widen and should be considered when interpreting pelvic X-rays. In the vertex presentation, the fetal head is usually located in the pelvis and the rest of the body, above the pelvic brim. Pelvic fractures in late gestation may result in fetal head injury (skull fractures, intracranial injuries) [49]. Differentiating between head trauma with convulsions and eclampsia (hypertension, proteinuria, and peripheral edema) as a cause of seizures is important [49].

There is an increase in the level of maternal plasma fibrinogen, as well as factors II, VII, VIII, IX, and X, and a decrease in plasminogen activator levels. This is important to remember in any trauma situation where hypercoagulability and the risk of deep venous thrombosis are already increased.

Table 10.3 "Normal" laboratory values during pregnancy

Hematocrit	32–42%
White blood cell count	5000–12,000/μL
Toxicology screen	Negative
Arterial pH	7.40–7.45
Bicarbonate	17–22 mEq/L
pCO_2	25–30 mmHg
Fibrinogen	264–615 mg/dL

The clinician should be aware of "normal" laboratory values during pregnancy (Table 10.3). Note that it is normal to have an elevated white blood cell count, slightly elevated arterial pH, decreased serum bicarbonate level and arterial pCO_2, and increased fibrinogen level. The finding of a normal nonpregnant value for pCO_2 or fibrinogen in the pregnant patient is especially concerning.

10.1.4.2 Fetal Physiology and Assessment

Fetal Physiology

During the first week, the conceptus has not yet implanted in the uterus, making it relatively resistant to injury. Soon thereafter, the embryo attaches to the uterus via the anchoring villi. The placenta is not as elastic as the myometrium, potentially leading to shear stresses and disruption of the villi when force is applied to the uterus. The well-being of the fetus is dependent on the adequacy of the maternal blood flow to the placenta, which is mainly derived from the uterine arteries. The uterine vascular bed is a low-resistance system, not capable of further dilation and devoid of autoregulation. Therefore, placental blood flow varies directly with the net perfusion pressure (uterine artery pressure–uterine venous pressure) across the intervillous space and inversely with uterine vascular resistance. In a normal pregnancy, there is a considerable functional reserve in the fetus to withstand changes in uterine blood flow or oxygenation. In sheep, fetal oxygen consumption does not decrease until the delivery of oxygen is reduced by approximately 50% [55]. Later in pregnancy, vital fetal organs such as the brain and myocardium are further protected by the "diving reflex," which allows redistribution of fetal cardiac output during maternal hypoxemia or compromised uterine perfusion. The response of the fetus to these insults is limited and seems to vary with gestational age. Decreased placental blood flow quickly leads to fetal distress.

The fetoplacental circulation contains around 110 mL/kg of blood [56]; at 30 weeks gestation, about 55 mL/kg is in the fetus, rising to 90 mL/kg at term. Therefore, premature infants have a lower blood volume with the consequences of hemorrhage being more dramatic. Maternal exposure to fetal blood cells during gestation is common, occurring in 95% of pregnancies. However, the volume of exposure is small with an estimation of less than 2 mL in up to 98% of exposures [57]. In rare cases, 0.3% of pregnancies, fetal hemorrhage (≥30 mL) occurs, and 1:2800 pregnancies are complicated by a catastrophic level of blood loss (≥150 mL) causing fetal hemodynamic instability [57, 58].

Fetomaternal hemorrhage (FMH) is described in the Sect. 10.3.5.6.

Fetal Assessment

The aim of the fetal assessment is to detect fetal distress and reduce the risk of fetal loss. Some authors have in the past been unable to identify any significant risk factors relating to injury or patient physiology that would predict poor outcome [59, 60]. A number of risk factors for fetal loss have been identified, including penetrating uterine injuries, severe maternal head injuries, and maternal pelvic fractures (Table 10.4). Fetal monitoring is described in the Sect. 10.3.7.4.

Table 10.4 Factors predicting fetal death in trauma [15, 33, 46, 54]

Ejection from vehicle
Pedestrian injury
Lack of restraints
Maternal tachycardia
Maternal hypotension
Maternal hypoxia
Maternal contractions
Abnormal fetal heart rate
Injury severity score >9

10.1.5 The Impact of Pregnancy on Trauma Mortality

The tenth revision of the International Classification of Diseases (ICD-10) defines a maternal death as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to, or aggravated by, the pregnancy or its management but not from accidental or incidental causes" [61].

Literature regarding hormonal influences on outcomes after trauma is abundant, yet findings have been contradictory. In experimental models, relatively high estrogen (and progesterone) levels have been beneficial with respect to immunomodulatory and vasodilatory effects and ultimate outcome (survival) after traumatic injuries [62, 63]. If a hormone-dependent survival benefit does exist, then pregnant women who have higher estrogen and progesterone levels might be expected to exhibit lower mortality compared with similarly injured nonpregnant women. Using the matching process, pregnant trauma patients are approximately 40% less likely to die than their nonpregnant counterparts [64]. This survival benefit was evident in younger women, suggesting a possible additive beneficial effect of youth and pregnancy. Of interest, there was no survival benefit in pregnant women when severely injured patient subgroups were compared (ISS >15, severe head injury, severe abdominal injury, or patients in hypotensive shock), suggesting that whatever advantage that pregnancy may confer may be limited. Also of note is the trend toward increased likelihood of death in pregnant patients with severe abdominal injury, a finding which may be related to placental abruption contributing to internal hemorrhage [64].

A study with data from the *National Trauma Data Bank* for the period 1994–2001 analyzed outcomes in 1195 pregnant trauma patients [12]. The crude mortality rate for pregnant patients who were injured was 1.4%, compared to 3.8% for nonpregnant patients ($p < 0.001$). Another study using a smaller dataset found that "pregnancy does not increase maternal mortality from trauma" and that the most frequent cause of death in injured pregnant patients was head injury [34]. However, there is no proof that estrogen and progesterone are responsible for the survival advantage of pregnant patients. Probably hemodynamic changes are responsible as well as more close observation of pregnant than nonpregnant patients.

10.1.6 Major Hemorrhage

10.1.6.1 Cardiopulmonary Resuscitation

Hypovolemia will manifest as thready pulses, tachycardia, flattened neck veins, pallor, and prolonged capillary refill. If a radial pulse is palpable, the systolic blood pressure is approximately 80 mmHg. The absence of carotid and peripheral pulses indicates pulseless electrical activity, and *advanced cardiovascular life support* (ACLS) protocols should be initiated. If there is a need to defibrillate the patient, standard ACLS voltage should be used (Fig. 10.3).

There is no evidence that the fetus is harmed by the current from defibrillation [65]. External fetal monitors should be removed before delivering shocks [65]. Chest compressions should be carried out with the understanding that the maternal heart is displaced upward in the chest by the gravid uterus at advanced gestations, and this should guide hand placement [65].

The cardiopulmonary resuscitation (CPR) should not be interrupted for the administration of medications because they get circulated with compressions [66]. Administration of medications in pregnancy through lower extremity lines should be avoided because they may not adequately reach the maternal heart because of compression by the gravid uterus [66].

Palpable femoral pulses have not been shown to be reliable indicators of blood flow during CPR because retrograde flow in the femoral vein could mimic femoral artery pulsations [66]. The presence of a carotid pulse during CPR is also not an indicator of adequate cerebral or coronary

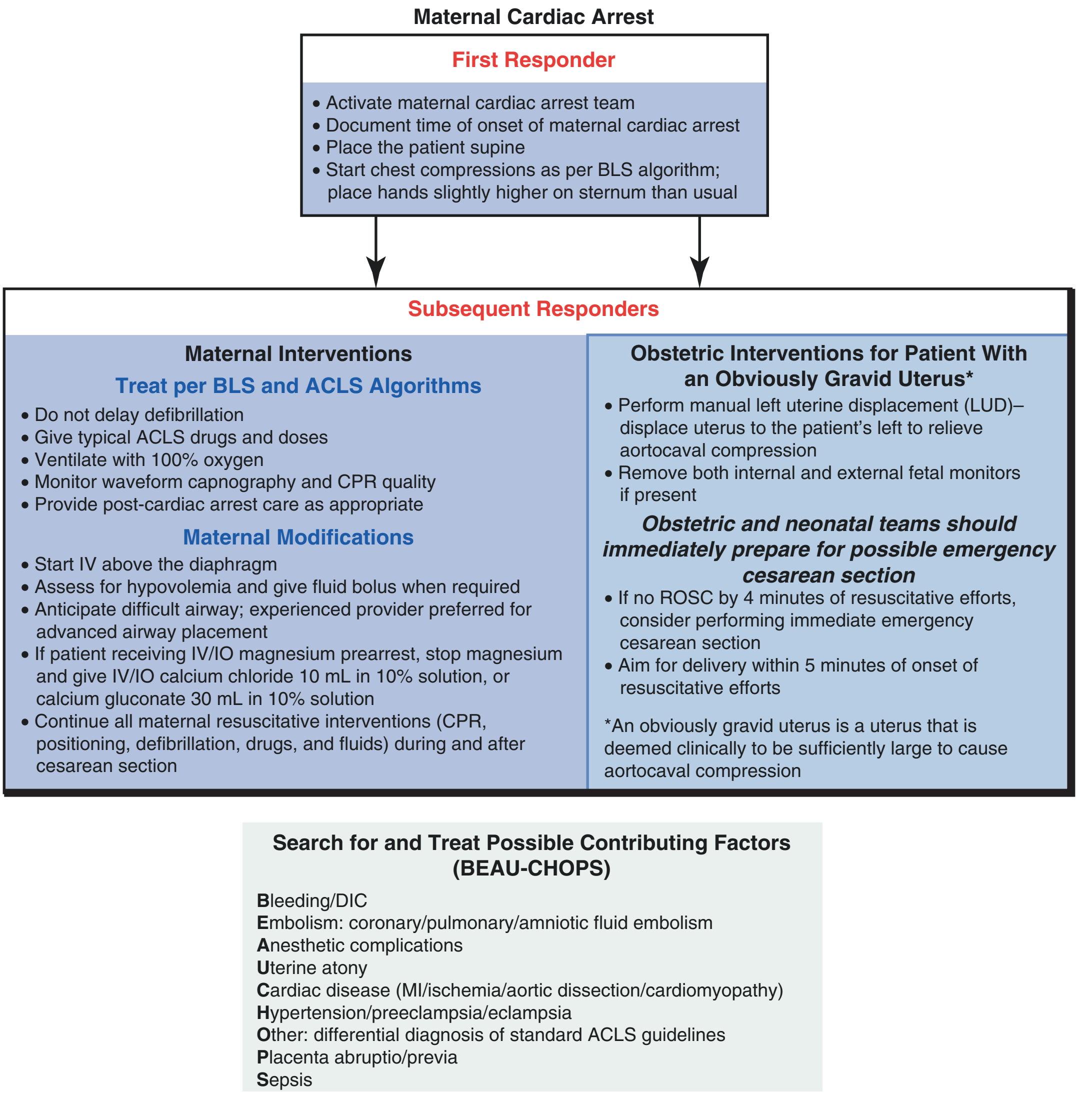

Fig. 10.3 Maternal cardiac arrest algorithm. Reproduced with permission from [65]

blood flow [66]. An end-tidal CO_2 monitor can be used as an indicator of adequate CPR efforts and the return of spontaneous circulation [66].

10.1.6.2 Major Hemorrhage

Major obstetric hemorrhage is defined as a blood loss of ≥2500 mL, transfusion of 5 units of red blood cells, or treatment of a coagulopathy [67]. Transfusion of blood and blood products in trauma and major hemorrhage is changing as a result of experience in military medicine. Resuscitation in obstetric hemorrhage is similar to that in trauma as both aim to stop bleeding, maintain efficient oxygen delivery, and prevent the development of the "lethal triad" of acidosis. Protocols for defibrillation and doses of medications are not changed in pregnancy. Obstetric resuscitation often starts with the administration of clear intravenous fluids and packed red blood cells (pRBC), following which the use of clotting products and platelets is considered, often guided by coagulation studies that delay treatment [68]. The *UK National Patient Safety Agency* recommends monitoring laboratory blood tests during massive transfusion but also that administration of blood and

blood products should not be delayed while awaiting results [67–69]. Resuscitation of bleeding patients with crystalloid, colloid, and plasma-poor pRBC at the same time when clotting factors are being consumed results in the concentration of plasma coagulation factors falling to <40% and typically occurs before 10 units of pRBC has been given [70]. Disseminated intravascular coagulopathy in obstetric hemorrhage can also occur early, especially if hemorrhage is not treated rapidly. Early treatment of massive hemorrhage after trauma using fresh frozen plasma (FFP) and pRBC in a 1:1 ratio, current practice in US and British military, is thought to improve survival [70–73]. Military guidelines for hemorrhagic shock also recommend administration of platelets in a 1:1 ratio with pRBC [71–73].

Prevention of coagulopathy should be better than its treatment and requires anticipation [70]. Some authors advise that replacement of clotting factors should be made on clinical grounds, rather than based on laboratory results [71, 73]. The *Association of Anesthetists of Great Britain and Ireland* guideline recommends an early infusion of FFP (15 mL/kg) to prevent hemostatic failure and may need to be started if a senior clinician anticipates massive hemorrhage [74]. This guideline emphasizes the importance of preventing hemostatic failure because, once established, standard regimens of FFP infusion are likely to be inadequate and larger volumes will be required with greater risk to the patient and cost implications for the hospital [74].

For massive obstetric hemorrhage, a ratio of 6:4:1 for pRBC/FFP/platelets has been suggested. If bleeding continues after initial treatment, consideration should be given to increasing the amount of FFP to give a ratio of 4:4:1 [69].

Point-of-care tests can measure hemoglobin concentration and the coagulation profile and may guide blood product replacement following initial resuscitation.

Fibrinogen concentrations are also greater in pregnancy; the optimal posttransfusion fibrinogen concentration has been suggested as 1.0–2.0 g/L [68]. The high ratios of pRBC to coagulation products that are recommended for other types of trauma may therefore not be required in the obstetric patient, whereas greater replacement of fibrinogen may be necessary. There is evidence to support 1:1:1 ratios of pRBC/FFP/platelets in trauma but less so in obstetrics [68, 71–73].

Maintenance of a platelet count of 50–100 × 10^9/L has been suggested although should only be used as a guide in conjunction with the patient's clinical condition [68]. pRBC/platelet ratios of 5:2 and 5:1 showed good results [68, 75]. Consensus guidelines suggest that recombinant factor VIIa (rFVIIa) should be considered before hysterectomy if hemostatic failure and hemorrhage continue despite optimal blood product replacement and obstetric management [68, 76]. Arterial thrombosis is a potential complication of rFVIIa use but has not been reported in a case series of 15 patients [76]. Its safety in the obstetric population is unproven, and it carries a significant cost implication. Using thromboelastography and thromboelastometry to guide optimum ratios of blood product replacement during obstetric hemorrhage may be limited by the time during the initial resuscitation phase, and there is limited familiarity with their use in obstetrics [67–69].

10.1.7 Prehospital Issues

The initial key to the survival of both mother and fetus is prehospital management. Pregnancy is considered a triage criterion for transport to a trauma center by the *American College of Surgeons Committee on Trauma*. Whenever possible, transportation should be to a center that is able to provide obstetrical care, as long-term monitoring is usually required for these patients. Goodwin and Breen [77] proved in a landmark contribution in 1990 that in addition to the accepted *Advanced Trauma Life Support* (ATLS) guidelines (first five on the list) for *transfer of patients to level I trauma centers*, there are four additional:

- Glasgow Coma Score <14
- Respiratory rate <10/min or >29/min
- Systolic blood pressure <90 mmHg
- Revised Trauma Score <11
- Anatomy or mechanism of injury
- Pulse >110 bpm
- Chest pain
- Loss of consciousness
- Third trimester

These criteria are particularly useful in mass casualty triage of patients in adjunction to prehospital trauma scoring systems in order to identify those patients who would benefit most from rapid transfer to trauma centers. In general, guidelines for adult prehospital trauma care also apply to pregnant trauma victims. Upon initial assessment, *emergency medical services* (EMS) should follow standard protocols like extrication with spinal immobilization and resuscitation as outlined in the ATLS guidelines. The decision to intubate the patient in the field is largely unaffected by pregnancy (see Chap. 21).

In the event of delivery, the neonatologist might be faced with a flaccid, apneic infant. Hence, it is pertinent to relate any prehospital use of medication by EMS to the receiving institution and trauma team. In general, the potentially catastrophic consequences of the patient losing her airway in the field or during transport usually justify acceptance of the minor risks associated with using paralytic and induction agents. Early establishment of a definite airway is usually the safest option.

Avoidance of the supine hypotension syndrome (uterocaval compression) should be a paramount part of all initial resuscitative measures in pregnant trauma patients. Placing the patient on a backboard with a 15° angle to the left is a pregnancy-specific intervention that should be employed in all patients beyond 20 weeks of gestation. Significantly decreased cardiac output of up to 60% due to uterocaval compression leads to prolonged resuscitation with increased acidosis and vasopressor requirements [78]. Below 24 weeks *manual left lateral displacement* might be sufficient. There is one-handed (Fig. 10.4a) and two-handed (Fig. 10.4b) technique according to the *American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care* from 2010 [65].

In gestations of >24 weeks, a 30° lateral tilt is recommended (Fig. 10.5). Although this reduces the efficacy of CPR compared to the supine position, in the pregnant patient, the slightly reduced efficacy of chest compressions is outweighed by improved cardiac preload and overall cardiac output [78]. Therefore, *Eastern Association for*

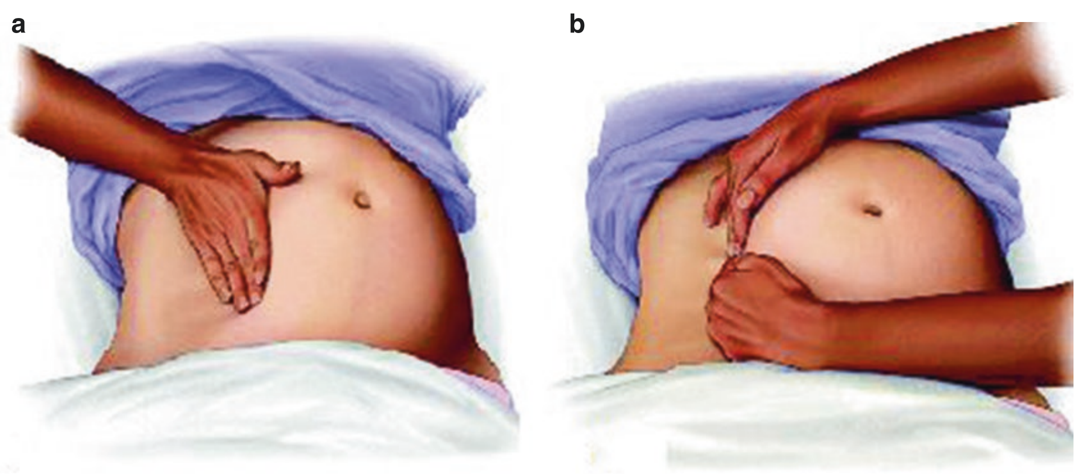

Fig. 10.4 Left lateral uterine displacement using (**a**) one-handed technique and (**b**) two-handed technique. Reproduced with permission from [65]

Fig. 10.5 Patient in a 30° left lateral tilt using a firm wedge to support the pelvis and thorax in gestations of >24 weeks. Reproduced with permission from [65]

Surgery and Trauma (EAST) guidelines recommend a left lateral tilt of at least 15° during the initial phase of resuscitation. Left lateral tilt can be achieved by placing a wedge under the right flank and hip, which in turn displaces the uterus to the left side.

Placement of a hard backboard in the supine position might not be tolerable for third-trimester gravida. The increased work of breathing due to increased diaphragmatic splinting might lead to respiratory failure. In this circumstance, transport in a 30° reversed Trendelenburg position seems acceptable [14]. As far as i.v. access routes in pregnant trauma patients are concerned, femoral access procedures should be avoided. Because of the risk of uterocaval compression, distribution of medication or fluids might be significantly altered when using the femoral route in pregnant patients.

Whenever possible, pregnant females should be transported rapidly to a designated trauma center that has the facilities for adequately managing both mother and fetus. The transfer should occur rapidly even in cases of minor trauma because of the high incidence of fetal demise even under these circumstances. Paramedics should seek information regarding pregnancy from female patients of childbearing age. A distended abdomen may be due to a gravid uterus or intra-abdominal bleeding. Pregnancy should prompt positioning of the patient in the left lateral decubitus position to avoid compression of the vena cava by the uterus and resultant hypotension and possible placental abruption which does not occur immediately after trauma but may result from placing an injured patient in the supine position [48]. In the supine position, in late pregnancy, the vena cava is completely obstructed in 90% of women, and venous return occurs through the azygous, lumbar, and paraspinal veins [79, 80]. The stroke volume and cardiac output increase by 30% when preterm pregnant female changes from the supine position to the lateral decubitus position [81]. Systolic blood pressure is maintained by an increase in peripheral resistance [79]; however, in the case of hemorrhage, this compensation is lost.

Should the emergency medical technician suspect a spinal fracture, a left lateral tilt position can be utilized. Oxygen supplementation by nasal cannula or face mask should be routine. In the event that prehospital transfusion is required, O-negative blood should be used whenever possible. Emergency medical services that still use the military antishock trousers (MAST) should be aware that it is contraindicated to inflate the abdominal portion of this device for pregnant women. Not only can this maneuver cause reduced uterine perfusion, but it also can increase the cardiac workload.

Appropriate personnel must be present or readily available at the emergency room when the emergency vehicle arrives. A team should be assembled that includes a neonatologist, anesthesiologist, trauma surgeon, sonographer, and staff radiologist. If a pelvic fracture or bleeding is suspected, a senior interventional angiographer should be notified immediately to be on standby.

10.2 Anesthetic Management

See Chap. 21.

10.3 Blunt Trauma

10.3.1 Incidence

MVAs, domestic violence, and falls are the most common causes of blunt trauma in pregnancy [4, 13, 18, 25, 32–34, 46, 51, 59]. In Australia, blunt trauma accounts for nearly all trauma during pregnancy (MVA, injuries to occupants 65–75%; falls 10–20%; motor vehicle collision, injuries to pedestrians 5–15%; assault 1–10%) [82, 83], whereas in the United States, penetrating injuries account for up to 10% [4]. Different mechanisms of maternal injury occur in pregnant women with blunt abdominal trauma compared with their nonpregnant counterparts. Because the gravid uterus changes the relative location of abdominal contents, transmission of force may be altered in the pregnant abdomen [15, 50, 84]. Before 13 weeks of gestation, the uterus is protected by the bony pelvis. Fetal loss in the first trimester is not secondary to any direct uterine trauma but usually is due to maternal hypotension, with hypoperfusion of the uterus and its contents or the mother's death. The direct fetal injury is extremely rare following blunt trauma, complicating <1% of all significant maternal trauma. Uterine rupture following blunt trauma in pregnancy is also rare occurring in 0.6% of cases. Distribution of all-cause blunt trauma in non-pregnant and pregnant patients is compared in Fig. 10.6 and mainly caused by MVAs in both groups.

10.3.2 Motor Vehicle Accidents

10.3.2.1 Introduction

Automobile crashes are the largest single cause of death for pregnant females and the leading cause of traumatic fetal injury mortality in the United States [10, 85]. Each year, 160 pregnant women die in MVAs, and additional 800–3200 fetuses die when the mother survives in the United States [86, 87]. According to research by the *National Highway Traffic Safety Administration* (NHTSA), in the United States, passengers who use seat belts in the back seat of vehicles have 44% more chance to survive a traffic accident than those travelers who are not tied. According to the same source, in 2006, there were 81% of passengers in cars tied with the safety belt in the United States, which according to NHTSA data saved 15,383 lives. However, research also shows that 37% of passengers died in traffic accidents, despite the fact that they were fastened by a safety belt. The reason for this is the inappropriate handling of the safety belt, which can result in fatal consequences. This was in particular expressed by the least-protected groups in transport, namely, children under 12 years of age and pregnant women. For these reasons, by legal requirements, the use of additional passive safety factors was prescribed for children less than 12 years, i.e., car seat. Because of that, in the final law on road traffic, safety requires that all children under 12 years must use a child safety seat adapted to their age unless they are transported to

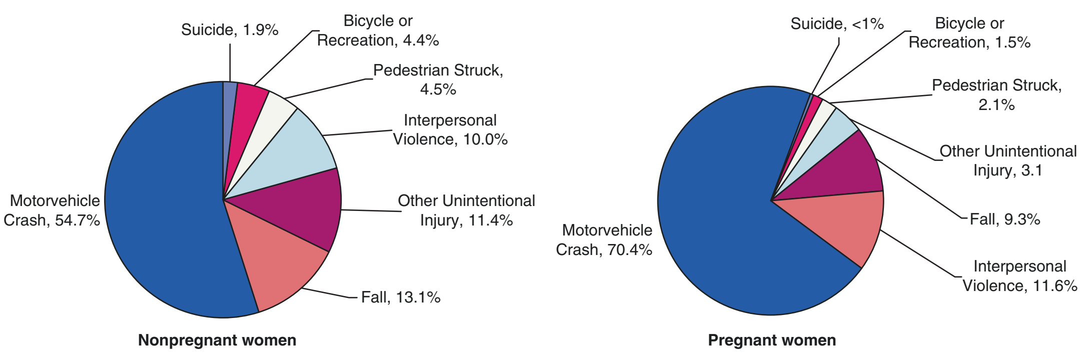

Fig. 10.6 Distribution of all-cause blunt trauma in nonpregnant and pregnant patients. Reproduced with permission from [12]

a place where there is a zone in the two-point binding. There is no legal framework for a pregnant woman that obliges them to undertake special measures when driving.

10.3.2.2 Incidence

In the United States, the annual crash rate for pregnant women has been estimated as at least 13/1000 person-years as compared with 26/1000 person-years among nonpregnant women [10]. However, one should use caution before presuming from these data that pregnant women are at lower crash risk. Identifying pregnancy status from crash and medical records is not always easy for crash investigators because early pregnancy cases may not be known or reported. Further, many women are not interviewed directly, resulting in reliance on written records that may or may not exist, especially for events that often do not result in hospital visits. Also, the methods for determining pregnancy and the completeness and accuracy of pregnancy status in National Automotive Sampling System/ Crashworthiness Data System (NASS/CDS) have not been externally validated. Furthermore, NASS/CDS coding rules state that when pregnancy status is unknown, cases are to be assigned to the "female not reported pregnant" category [88]. There is evidence from a statewide injury inpatient study that the hospitalized crash injury rate of pregnancy-associated cases is not lower compared to that of all women of reproductive age (even after a length of stay adjustment) [29].

With more women driving and driving more miles today than two decades ago [89], it has been estimated that about 2% of all live births in the United States, or 79,000 children (26/1000 person-years), are exposed in utero to a police-reported crash [10]. For comparison, the NHTSA reports that there are only about 23,188 infants reported in crashes each year (6/1000 person-years) [10]. Given the potential numbers of exposed fetuses, longitudinal research on nonfatal fetal outcomes is needed. Fetal trauma exposure has received very little attention among reproductive and environmental scientists and funding agencies. This is mainly due to the following: (1) major deficiencies in the way fetal trauma-related deaths are coded in vital statistics, (2) the lack or poor quality of pregnancy status variables and follow-up in most injury surveillance systems, (3) unfamiliarity by many reproductive health researchers with injury science and the large societal burden of injury, and (4) the difficulty of attributing adverse birth outcomes and developmental problems many months or years after trauma. However, the recent convergence of several research lines suggests reasons why this problem should receive urgent attention.

10.3.2.3 Mechanism of Maternal Uterine Trauma and Fetal Trauma

The first experimental research was on the savannah baboon (*Papio cynocephalus*), chosen because the uterine and placental anatomy is similar to that of the human [90]. The injuries observed are similar to those reported in automobile accidents involving pregnant women [91, 92]. The fetal death rate of 8.3% among maternal animals impacted with three-point restraint was significantly lower from 50% among maternal animals impacted under lap belt restraint alone [93]. There is a remarkable increase in uterine pressure during impact. The maximum pressure observed was approximately ten times that observed during labor [94]. Simultaneous recordings of abdominal pressure during impact show that the uterus was not protected from rupture by an equal but opposing pressure within the surrounding abdominal cavity [95]. Nor was there a decrease in uterine pressure during impact when forward flexion was prevented by shoulder restraint or rearward facing impact. The findings also indicate that the gravid uterus is capable of withstanding extraordinary pressures of short duration and that such pressures are produced by deceleration with or without subsequent body flexion. Maternal response to impact consisted of transient depression and bradycardia. The former resembled mild cerebral concussion. Postimpact bradycardia occurred only with violent motion/ deceleration of the body. This phenomenon is attributed to increased vagal tone secondary to acute hypertension in the carotid sinus. This

effect can be abolished by atropine and occurs only when there is the rapid forward motion of the head and neck [96].

In experimental crashes, pregnant baboons were placed in two-point restraint in a Hyge sled accelerometer which simulates an automobile crash under conditions of rapid deceleration (Figs. 10.7 and 10.8). A biphasic increase in intrauterine pressure is experienced. The first increase results from sudden deceleration of the pelvis stopped by the lap belt. At the same time, the uterus continues to move forward striking the anterior abdominal wall. This results in an increase in intrauterine pressure approaching 500 mmHg. Later during this crash sequence, the upper torso of the animal is thrown forward essentially collapsing around the pregnant uterus creating the second increase in intrauterine pressure, approaching 550 mmHg. From this and other experiments with animals held by three-point restraints (*lap belt* and *shoulder belt*), it is clear that the second increase in intrauterine pressure can be eliminated by preventing the torso from collapsing around the pregnant uterus. This results in a decrease in fetal mortality from 100% to 40% [97].

The first important research line comes from reports by the NHTSA and others, which have shown that in the period 1975–1990, primarily because women are driving more miles, the number of fatal crashes involving female drivers has increased dramatically by 62% [89]. This large increase in exposure may have resulted in a poorly documented trauma-induced epidemic of fetal loss, fetal injury, and adverse reproductive outcomes. While there is indirect corroborating

Fig. 10.7 The experimental research on the savannah baboon delivered the first knowledge of maternal and fetal physiology during and after motor vehicle accidents with belt restraint. Reproduced with permission from [90]

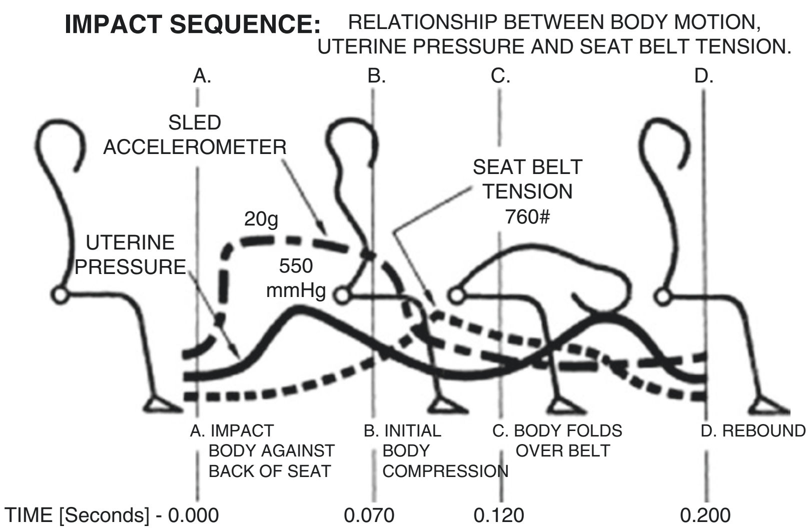

Fig. 10.8 Impact sequence (see test for details). Reproduced with permission from [90]

evidence from national vital statistics data of similar increases in neonatal deaths due to maternal trauma during this time span [98], there is currently no way of confirming this because of the documentation problems mentioned above.

The second research line emerges from looking at the relationship between stress reactions and preterm labor. Although much of this work has focused on the stress of poverty, abuse, and social disparities, trauma itself is a widespread but often overlooked trigger of high levels of stress. It has recently been estimated that 9% of survivors of serious crashes develop significant post-traumatic stress symptoms and that many other survivors have post-traumatic stress disorder-like reactions [98]. In fact, MVAs may be the leading cause of post-traumatic stress disorder, providing fertile opportunities for stress/reproductive research. One thread suggests that stress either very early in pregnancy or in the 24–28th weeks of pregnancy leads to a twofold increase in the risk of autism [99]. Since autism is usually not apparent until a child is 1–3 years of age, it may be difficult to trace back to the original events. Also, experiencing a stressful event during the periconceptional period was associated with increased congenital anomalies including heart and neural tube defects and cleft lips and palates [100].

The third research line comes from cohort studies of hospitalized injured pregnant women that linked to birth records. Wolf et al. reported in a 1980–1988 retrospective cohort study of seat belt use and pregnancy outcome after MVAs that unrestrained pregnant women were more likely to give birth to a low birth weight baby and more likely to give birth within 48 h after the MVA than restrained pregnant drivers [40]. One retrospective cohort study showed pregnancy outcomes from hospitalized injury of all types in Washington State in the period 1989–1997 [98]. It reported increased risks for placental abruption, low birth weight, prematurity, and fetal death.

The fourth line of research focused on the risk of fetal mortality versus infant mortality from MVAs. Fetal motor vehicle injury mortality rates were much greater than that of infants [101].

The fifth research line is not as strong because the evidence of harm does not come from population-based studies, but from several case series. Seven mothers had MVAs; two had blunt abdominal trauma. Later clinical symptoms in the nine children included movement disorders and cerebral palsy among other findings [102, 103].

The issue of trauma as a true teratogen was raised (defined by the US Environmental Protection Agency as "The introduction of non-hereditary birth defects in a developing fetus by exogenous factors such as physical or chemical agents acting in the womb to interfere with normal embryonic development"). The most comprehensive study on the subject delivered the data found in the Tables 10.5 and 10.6.

Severe fetal injury can result from blunt trauma to the abdomen even in the absence of uterine injury, especially in advanced pregnancy. In early pregnancy, the uterus is protected by the bony pelvis and by the amniotic fluid which acts as a hydraulic shock absorber, decreasing the force of the blow by transmitting it equally in all directions: later in pregnancy the fetal head is fixed in the pelvis, and the buffering effect of the amniotic fluid is decreased, making the head prone to injury. Depressed skull fractures occur as the result of the contact of the skull against the promontory of the sacrum [104]. Skull fractures with intracranial hemorrhage appear to be the most common fetal injuries resulting from blunt trauma [105]. These fetal injuries as a cause of death can be present without evidence of placental separation, uterine trauma, or maternal shock.

The importance of MVAs as a cause of pregnancy loss has been largely ignored as a public health problem. Published estimates of the number of fetal losses caused by MVAs each year in the United States range from 1500 to >5000 [50]. Although some suggest that these estimates may be somewhat high, it seems clear that the number is significantly greater than the number of infant deaths caused by MVAs and that it probably exceeds the total number of children aged 4 years and younger died in MVAs [106]. Although many clinical protocols have been published for managing trauma during pregnancy [59, 77, 107], few studies have evaluated how to prevent fetal loss

Table 10.5 Rate calculations between women ages 15–39 in crashes by pregnancy status, *National Automotive Sampling System Crashworthiness Data System*, 1995–1999[a]

Rate calculations	Reported pregnancy status	
	Pregnant	Not pregnant
Annualized age-specific rate per 1000 live births (using 1997 live births as denominator)		
15–19 (n = 7478, SE = 3265)	15	NA
20–24 (n = 8230, SE = 2187)	9	NA
25–29 (n = 8850, SE = 10,048)	8	NA
30–34 (n = 6164, SE = 1737)	7	NA
35–39 (n = 2088, SE = 558)	5	NA
All ages (n = 32,810, SE = 12,585)	9	NA
Annualized age-specific rate per 1000 person-years (assuming pregnancy is detectable over 8 months)		
15–19	23	44
20–24	13	35
25–29	12	22
30–34	10	18
35–39	8	18
All ages	13	26

[a]Numbers and rates derived from weighted estimates unless otherwise stated
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Table 10.6 Selected comparisons between women ages 15–39 in crashes by pregnancy status, *National Automotive Sampling System Crashworthiness Data System*, 1995–1999[a]

Selected comparisons	Reported pregnancy status			
	Pregnant		Not pregnant	
	No (%)	SE	No (%)	SE
Number of cases, 1995–1999 (unweighted)	427	–	11,972	–
Annualized number of cases (weighted)	32,810	12,585	1,251,269	127,522
Number (% within age group) that were drivers				
15–19	5370 (72)	2731	217,584 (55)	38,104
20–24	5482 (67)	1671	222,105 (76)	39,222
25–29	5654 (64)	9746	164,136 (81)	10,816
30–34	4438 (72)	1284	137,751 (75)	18,767
35–39	1872 (90)	542	147,268 (83)	13,939
All ages	22,816 (70)	11,662	888,843 (71)	106,928
Treatment level (% within group)				
No treatment	7908 (24)	2868	635,197 (51)	76,723
Transport and release/treated at scene	19,217 (59)	10,546	422,593 (34)	60,488
Hospitalized or fatal	4431 (14)	1345	57,857 (5)	13,092
Other or unknown	1254 (4)	750	135,622 (11)	11,387
Total	32,810 (100)	12,585	1,251,270 (100)	127,522
Police reported belt use				
None used	4395 (14)	1696	158,021 (13)	42,023
Lap and shoulder	19,805 (59)	10,546	704,779 (59)	79,038
Lap or shoulder	824 (3)	391	29,280 (2)	5916
Belt used, type not specified	5716 (18)	3162	240,731 (20)	155,053
Other response	68 (0)	59	1321 (0)	284
No police indication	1970 (6)	628	57,585 (5)	18,588

[a]Numbers and rates derived from weighted estimates unless otherwise stated
Reproduced with permission from [10]

by improving safety restraint systems or vehicle design. In order to determine the pregnant occupant crash exposure, the NASS/CDS searched all crashes involving pregnant occupants between 1993 and 2003 [108]. Distribution of impact direction according to the sitting position is presented in Fig. 10.9.

In 1996, the first pregnant crash dummy was developed as a feasibility project [109]. Although

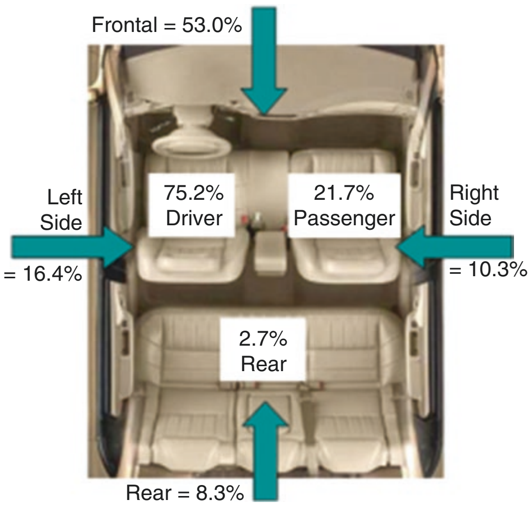

Fig. 10.9 Occupant seating position and impact direction distributions for pregnant occupants. Reproduced with permission from [108]

that project was an important first step in developing a pregnancy surrogate, the design has numerous limitations. In particular, the first-generation pregnant crash test dummy does not provide for assessing the likelihood of fetal loss as a result of the separation of the placenta from the uterus, which is believed to be the most common cause of fetal loss from abdominal trauma. In addition, the abdomen of the first-generation pregnant crash dummy does not have a realistic external contour and is too stiff. These deficiencies are likely to cause inappropriate interactions of the pelvis and abdomen with occupant restraints and vehicle components such as the steering wheel rim (Fig. 10.10). However, due to the difficulties in measuring this mechanism in the pregnant dummy, such as tissue strain and pressure, a computational model of the pregnant occupant was created [110]. This computer model has been used to evaluate frontal crashes and has shown that local uterine compression is a critical factor in predicting placental abruption [111].

10.3.2.4 The Seat Belt for the Prevention of Maternal–Fetal Injury

The first patented "safety" belt, designed to allow free movement and personal protection "for tourists," was granted to Edward J. Claghorn

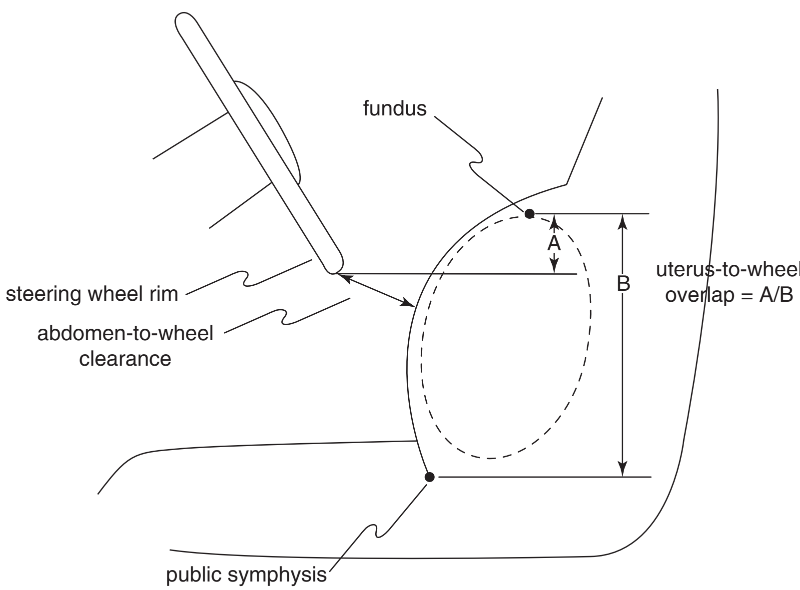

Fig. 10.10 Illustration of abdomen-to-wheel clearance and uterus-to-wheel overlap. Reproduced with permission from [37]

in 1885. It consisted of an inner and an outer belt. Although no use of this belt has been reported, some of the first gasoline-engine vehicles are believed to have been equipped with restraining belts to keep passengers in their seats when traveling over the rough and rutted roads of that time.

The seat belt is safety harness designed to secure the occupant of a vehicle against harmful movement that may result from a collision or a sudden stop. As part of an overall occupant restraint system, seat belts are intended to reduce injuries by stopping the wearer from hitting hard interior elements of the vehicle or other passengers (the so-called second impact) and by preventing the passenger from being thrown from the vehicle. Studies of automobile accidents from the 1960s have shown that the major single cause of fatal injury was ejection from the vehicle [112]. When the body is ejected, injury occurs as it strikes the ground or is crushed by the vehicle. Huelke and Gikas estimated that 80% of fatally injured automobile accident victims would have survived had they been wearing lap belts [112]. As a result, lap-type seat belts become standard car equipment in the 1970s [91].

Seat belts could reduce injuries by 51% [113], lap belts by 35%, and diagonal belts by 60–80% [114]. In Michigan, 80% of fatal accidents would have survived if they had been wearing only the lap belt [112]. Previous calculations found 35% fewer major, fatal injuries in seat belt wearers [115]. The outcome for the fetus is improved by the use of shoulder restraints. In a study of 22 baboons in the third trimester of pregnancy, an impact sled with a deceleration of 24.5–29.0 G-force was used to compare the effectiveness of lap belts and shoulder harnesses [97]. A significant difference in the fetal death rates was found, with 8% when a shoulder harness was used and 50% when a lap belt was used. There were no maternal deaths or instances of uterine rupture. The improvement in fetal survival with the use of a shoulder harness was due to the greater surface area over which the decelerative force was dissipated as well as the prevention of forward flexion of the mother.

> Pregnant women should be encouraged to wear properly positioned safety restraints throughout while riding in automobiles.
>
> *American Medical Association Committee on Medical Aspects of Automotive Safety*, 1972 [116]

> The three-point restraint system (that places the lap belt under the abdomen and across the upper thighs and the shoulder belt between the breasts) should be used by pregnant occupants.
>
> *American College of Obstetricians and Gynecologists, 1983* [117]

Using the seat belt prevents hitting the windshield with the head and the chest cage in the steering wheel. When a vehicle attacks a barrier with a speed that is realistic in the road traffic, the vehicle in a short time will void its speed, and the untied traveler will continue to move in almost the same direction and speed; during the mentioned attack—inside the vehicle—serious or fatal injury can occur. The safety belt is designed to keep the human body in the seat during the crash, meaning that it does not allow the body to strike inner parts of the vehicle or ejection of the body from the vehicle under the influence of created forces. Safety belts are most effective in frontal collisions or when a vehicle attacks the barrier. Researchers have shown that under the crash speed of about 50 km/h, the front is shortening by 50 cm, and a significant part of the load is taken by seat belts. In the sidelong collisions, the safety belts are much less efficient, and such collision leads to injuries of the head while hitting the side glass.

There currently are four principal configurations of seat belts in automotive use: the lap belt, the single diagonal belt, the three-point (or combination of lap and diagonal), and the double parallel combination of lap and double shoulder harness (Fig. 10.11).

Lap belt refers to a single belt across the anterior aspect of the pelvic structure; *seat belt* refers to any combination of lap and torso restraint. There are numerous variations of the types, such as five-point, double vertical belts without lap belt, and shoulder belts with inertia reels. Diagonal seat belts that run over the shoulder

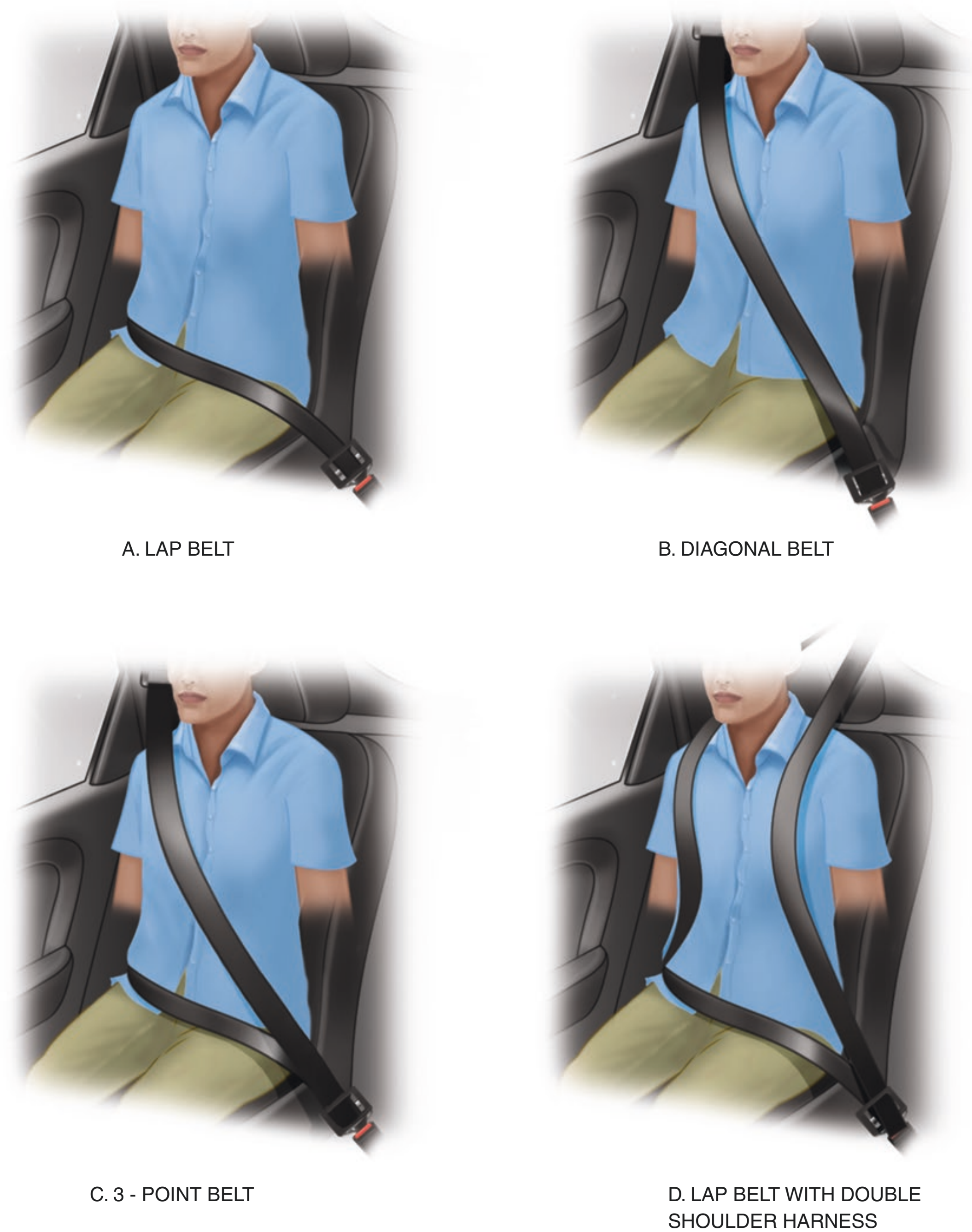

Fig. 10.11 Four basic restraint systems currently used in automotive vehicles. (**a**) A two-*point belt* attaches at its two endpoints. (**b**) A "sash" or *shoulder harness* is a strap that goes diagonally over the vehicle occupant's outboard shoulder and is buckled inboard of his or her lap. (**c**) A three-*point belt* is a Y-shaped arrangement, similar to the separate lap and sash belts but unitized. Like the separate lap-and-sash belt, in a collision, the three-point belt spreads out the energy of the moving body over the chest, pelvis, and shoulders. (**d**) *Lap belt with double shoulder harness* is improved three-point belt which further spreads out the energy of the moving body over larger body area. Reproduced with permission from [91]

cause injuries that are primarily confined to the upper part of the trunk such as bruised chest, fractured ribs or sternum, and a lacerated liver. There are fewer head and neck injuries with this type of belt than with the lap type. Injuries to the pelvis, lumbar spine, and abdomen are found with the lap-type belt. Bone injuries consist of fracture of the pubis, separation of joints, and compression fracture of the lumbar spine, the so-called fulcrum fracture [118].

The use of a lap belt alone may allow enough forward flexion and subsequent uterine compression to rupture the uterus. Placental abruption is believed to occur when the strain in the uterine wall exceeds 60%. The risk of placental abruption is largest for high strains that occur near the placenta which can be dramatically influenced by the lap belt position. Simulations have demonstrated that the vertical position of the lap belt can increase fetal risk by a factor of three (Fig. 10.12).

As the lap belt approaches the height of the placenta, which is located at the top of the uterus, the observed strain increases for a given crash pulse. Simulations with the lap belt directly loading the uterus at the placental location produced the highest recorded strain and likewise may rupture it [120]. Once the lap-belt height is above the placenta, the strain decreases with the strain for the top belt position matching that seen for the recommended belt location. However, there is increased risk to the mother with incorrect lap-belt placement, including elevated head and chest injury response. This is important because the best way to protect the fetus is to protect the mother.

The lap belt should be placed under the gravid abdomen, snugly over the thighs, with the shoulder harness off to the side of the uterus, between the breasts and over the midline of the clavicle [37]. Seat belts placed directly over the uterus can cause fetal injury [121]. It was shown that the three-point belt and the four-point belt were superior in protecting the pregnant occupant by reducing the movement toward the far-side door and therefore eliminating the head-strike potential. However, this resulted in some force being applied to the abdomen, and therefore it increased the risk of fetal injury. This is an acceptable trade-off given the most important factor in saving the fetus' life is keeping the mother alive. The reason that the four-point belt is better than the three-point belt with respect to abdominal loading is that some of the overall load is applied through the mother's neck and therefore less is applied to the abdomen in order to restrain her for the same given crash speed. The belt contact loads through the neck were below published injury thresholds [108]. Overall, the results indicate for all frontal and side impacts that it is safest for the pregnant occupant to ride in the passenger seat while wearing a three-point belt, or four-point belt if possible, and utilizing the frontal airbag when appropriate [110].

Additional improvements lead to seat belts with larger areas for better impact absorption

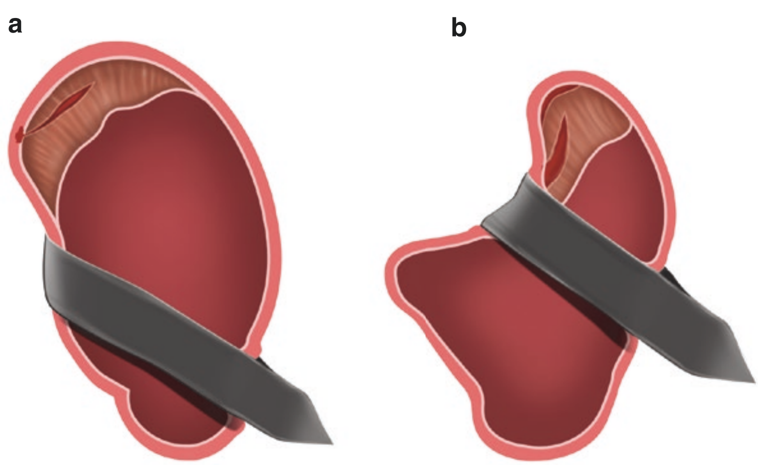

Fig. 10.12 Simulations at 35 kph showing uterine compression for the correctly positioned lap belt (**a**) and the incorrectly positioned belt (**b**) causing uterine fundal compression. Reproduced with permission from [119]

Fig. 10.13 (*Left*) Advanced restraint (mesh webbing) for the pregnant occupant that can be added to a standard three-point belt for maximum fetal protection (Reproduced with permission from [119]) or (*Right*) seat belt airbag reduces direct seat belt trauma (Reproduced with permission from [122])

further minimizing maternal and fetal injury. One includes a *mesh webbing* over the entire abdomen proved to be the best protective measure for the fetus. Another is seat belt airbag (Fig. 10.13).

The Seat Belt Syndrome

Distinctive injuries caused by safety belt due to traffic accidents were coined as the *seat belt syndrome* [115]. Rubovits in 1964 first reported the traumatic rupture with avulsion of the uterine musculature at the site of the seat belt impact. This was attributed to the force of the belt at the anterior uterine wall being transmitted to the fetus, which was then blasted through the left uterine wall [95]. This was fatal to the fetus. The absence of sign of shock or intraperitoneal hemorrhage precluded diagnosis for 2 days. Therefore, the disadvantages of using seat belts are most often related to injuries that it can cause during a collision. Injuries caused by the seat belt are most likely as follows [123]:

- Abdominal organ damage
- Bowel rupture
- Abdominal wall injuries
- Ruptured liver
- Blood vessel trauma
- Chest trauma
- Fractured sternum
- Myocardial contusion
- Spine fractures

There are countries like Japan where the pregnant women while driving are exempted of use of the belt [10] due to the possibility of fetal injury during sudden braking. It is important that pregnant women wear their seat belt to prevent secondary collision with interior structures of the vehicle or sudden ejection, to dissipate the force of an impact [124], and to provide both the mother and the fetus with maximum protection. But the seat belt must also be worn correctly to prevent potential significant harm to both the mother and fetus. Women are reported to be at an increased risk for intra-abdominal injuries or uterine rupture if restraints are improperly positioned at the time of collision [125]. In 1992, ACOG recommended that all women receive seat belt counseling from prenatal care providers. Nevertheless, many pregnant women report uncertainty about the safety and use of seat belts during pregnancy [126] and lack of information regarding proper seat belt use and its role in protecting the fetus [127]. If women regularly and correctly wear their seat belts, prenatal counseling on seat belt use during pregnancy would not be an important public health issue, but that is not the case. A 2004 study reported that only 45% always wear their seat belts (both before and during their current pregnancy) even though 72.5% of subjects were able to demonstrate the proper way to wear a seat belt [127]. In addition, only 58% thought that seat belts would have a positive effect if they were in an MVA during pregnancy,

34% were unsure of the effect, and 8% thought the seat belt would cause them to get hurt [127]. When asked if a seat belt would help protect their baby in the event of a crash, only 55.3% of the women thought that the seat belt would help, 10.7% said it would do harm, and 34% were unsure [127]. The women who thought a seat belt would help protect them were significantly more likely to report always wearing a seat belt versus the women who were unsure or thought negatively of the seat belt (84.4% vs. 64.6%) [127]. Considering this finding, it seems that knowledge and belief in the effectiveness of the seat belt could help motivate women to use a seat belt. Therefore, prenatal care providers should take the opportunity that prenatal visits provide to educate women on the importance of proper use of seat belts during pregnancy to protect both the mother and fetus and the hazards of crashes during pregnancy [128], as well as clear up any misconceptions that a woman may have about seat belt use. However, several questions remain. For instance, what percentage of women are actually receiving seat belt use counseling, how many wear their seat belts during pregnancy, and how many of them report being hurt in an MVA? A recent study from Hong Kong showed that 76.6% of pregnant women reported using a seat belt in the 6 months before pregnancy, but compliance was reduced as the pregnancy progressed. Seat belt use was reduced to 73.5% in the first trimester, 70.5% in the second trimester, and 67.1% in the third trimester. The most common reasons for not using seat belt were: not useful (12.6%), causes discomfort (89.1%), and may harm the fetus (45%) [129].

Seat Belt Use Counseling

Prenatal care provider counseling for seat belt use occurred in 48.7% of prenatal visits; women aged 20–29, nonwhite, Hispanic ethnicity, and less educated were the most likely to report being counseled on seat belt use; women who were 30 or older and had a greater than high school education were more likely to report always wearing seat belts in the last trimester; and on average, 2.3% of respondents reported being hurt in a “car accident” during pregnancy. Women less than 20 years old, of black race, and less educated were the most likely to report being hurt in a crash during pregnancy. It is encouraging that this study determined that black women are the most likely to report being counseled on seat belt use during pregnancy because this study also determined that black women were more likely to report being hurt in a crash. Although there are groups of women who are more at risk for experiencing a crash during pregnancy, it has been demonstrated that less than half of women always wear their seat belt (including before and during pregnancy) [127]. For this reason, all women should be counseled on the importance of seat belt use and how to properly wear a seat belt during pregnancy regardless of age, race, ethnicity, or education.

Extrapolating from the reported *Pregnancy Risk Assessment Monitoring System* (PRAMS) rates in 2001 to the US population, it is estimated that at least 92,500 pregnant women (2.3/100 live births) are hurt in MVAs each year in the United States. This finding is important because it is one of the few such estimates available from population-based multistate data sources. The only previous estimate came from analysis of crashes reported by the NASS/CDS from the period 1955–1999 [10]. The latter reported only about 33,000 pregnancy-related crashes (not injuries) annually. The current PRAMS data portrays the magnitude of the level of underreporting in the NASS data system because by definition, pregnancy status is 100% complete in PRAMS. The findings regarding seat belt counseling were similar to the findings of earlier studies. The percentages of women who reported being counseled were 48.7% in 22 PRAMS states, 53% in 14 PRAMS states during 1997 and 1998 [130], and 48% in 19 PRAMS states in 2000 [128]. The consistently low prevalence of seat belt use counseling during pregnancy suggests that this issue has not yet been properly addressed. Interventions need to be put in place to ensure that women are educated and counseled on the importance of and proper use of a seat belt during pregnancy. Prenatal counseling is a time where topics related to the health of the mother and the baby are discussed and proper seat belt

use should be included. It is important to note that the literature is not unanimous on whether prenatal counseling is the best way to increase the use and proper use of seat belts during pregnancy. It is particularly important for those women identified as being more at risk for adverse pregnancy outcomes (young women who smoke do not begin prenatal care during the first trimester and have not completed high school).

One issue with seat belt counseling during pregnancy is that some women have been reported to forget some of the topics that were discussed during prenatal counseling, including seat belt use. Tyroch et al. did a follow-up survey in pregnant women after their initial prenatal visit and showed that 73% of the women did not recall having received advice on seat belt use even though they received brief counseling by a clinician and a pamphlet on seat belt use during pregnancy during their initial visit [131]. The new teaching methods such as audiovisual aids, mannequins, or having women demonstrate proper seat belt use to the health-care provider may increase knowledge retention [131]. However, among the population in general, some research suggests educational initiatives have been ineffective at increasing seat belt use when compared with successful legislative and enforcement efforts [132]. On the other hand, several studies have reported positive effects due to prenatal counseling. For instance, Pearlman and Philips administered a survey to women who consecutively presented for their first prenatal visit and readministered the survey at their second visit (28–32 weeks gestation) to assess the attitudes toward and usage of lap and shoulder belts. The authors showed that women who received seat belt use instructions were more likely to use restraints and properly identify restraint position than those who received no information [133]. Similar findings were reported by Johnson et al. for pregnant women who recalled being advised on correct placement [134]. Thus, studies show that education by prenatal care providers increases the number of pregnant women correctly using seat belts [39, 133, 134]. Therefore, instruction by health-care providers is an important component to solving the problem of incorrect seat belt placement [134] and lack of use among pregnant women. This study is not without several limitations due to the way that PRAMS collects data. The first limitation is a potential misclassification. Since it has been shown that some women forget about counseling [131], it is possible that some women are misclassified as never having received prenatal counseling on seat belt use in the PRAMS data, when in fact they did. Another limitation is potential recall bias due to the fact that PRAMS collects data from women within 2–6 months postpartum. This means that some women are asked to recall counseling information and topics that were provided or discussed potentially over a year before the data were collected and those who had uneventful pregnancies may be less likely to remember specific counseling topics. Future research is needed to determine the effectiveness of different educational strategies [123]. Another limitation of this study is that out of the 22 states in this study, only Maryland and Vermont collected data on seat belt use during pregnancy and the data they collected is only for the last 3 months of pregnancy. This limits the generalizability of the seat belt use data not only for women in those two states but also to only women in their third trimester of pregnancy. Seat belt use might change as a woman's pregnancy advances due to the growing abdomen and increasing level of discomfort.

Comparison of Belted and Unbelted Pregnant Women

There is only one study with comparison of belted and unbelted pregnant population during MVAs with short- and long-term follow-up [38]. The main findings are that nearly 3% of births linked to MVAs during pregnancy and that pregnant women in crashes in which the mother wore her seat belt were not significantly more at risk for adverse fetal outcomes than pregnant women not in crashes. Pregnant women who did not wear seat belts during a crash were more likely to have:

- Low birth weight infant
- Excessive maternal bleeding
- Three times higher incidence of fetal death

Authors found that 2.8% of all live births in the state were from mothers who were exposed

to a driver-related MVA during pregnancy. Considering the absence of data on nondrivers and nonreported crashes, this suggests that in Utah more than 3% of all live births are from mothers exposed to an MVA. The only other study known to estimate the rate of MVA exposure during pregnancy reported it as 1% based on investigator reports from the NASS/CDS and was thought to have underestimated [10]. Although belt use has been shown to be effective in reducing morbidity and mortality for the mother and the fetus when comparing belted and unbelted pregnant women [40, 97, 135], this study extends these findings by showing that belted pregnant women in crashes were not significantly more at risk for adverse fetal outcomes than pregnant women not in crashes. No other studies have compared crash-related pregnancy outcomes with a noncrash population. Klinich et al. found that the odds of the adverse fetal outcome, including fetal loss, preterm delivery, placental abruption, and uterine laceration after an MVA were 4.5 times higher among women who were not properly restrained compared with those who were properly restrained at the time of the crash [136].

Compared with uninjured pregnant women, injured pregnant women are at increased risk of several adverse obstetric outcomes, including placental abruption, prematurity, low birth weight, fetal distress, and fetal death [137]. However, the study only included women who had been hospitalized for their injuries and delivered during their hospital stay, which would indicate an overall greater severity of injuries. Because the study also focused on all injuries, and not just MVA, the authors were not able to control for severity-reducing countermeasures such as seat belt use. Lack of seat belt use has previously been associated with low birth weight with documented and increased risk of delivery within 48 h of the crash [40]. There is no increased risk of immediate delivery. Unbelted pregnant women were nearly three times more likely to experience fetal death than belted pregnant women in crashes. Even though the small numbers of fetal deaths in the study by Hyde et al. limited the ability to more completely describe the effect of MVA risks of fetal death, the crude OR of 2.8 was an indication that the unrestrained pregnant women were much more likely to lose their fetus in an MVA than restrained women. Some did not find a statistically significant increase in the risk of fetal death associated with lack of seat belt use [40]. A population-based study published over 40 years ago reported that lap belt use was associated with a reduction in maternal death and maternal injury, but there was no association with fetal loss [135]. The majority of fetal deaths (51%) were linked to crashes that occurred during the first trimester, even though all of the fetal deaths occurred during the second and third trimesters. This may be a result of the fact that first trimester crashes have up to 36 weeks to result in a fetal death, whereas the other trimesters have correspondingly less time to do so. Essentially, there was a longer exposure period of gestation in which fetal deaths could occur, whether or not those fetal deaths were related to the crash. Another possibility is that the last trimester may be offset by an increased likelihood of these infants being born through trauma- or physician-induced labor, which may have resulted in deaths not recorded in the fetal death file. Finally, the finding may suggest that the first trimester represents a sensitive period of fetal development and vulnerability to crashes but that the fetal deaths do not occur (or are not noticed) until a few weeks later in development. Further research is warranted to better determine how gestational age impacts fetal death due to crashes. Also, there is an increased risk of fetal death for unbelted crashes that occur during the later weeks of gestation. When comparing gestational age and the time of fetal death, the unbelted group had sharp increases in fetal deaths during 31–38 weeks of gestation. This may be indicative of a period of increased vulnerability to fetal death from MVA among unbelted drivers. One might believe that this increase is a result of more crashes during the third trimester. However, linkage of all births involving unbelted MVA showed that only 25% of crashes occurred during the third trimester, the lowest percentage of any trimester. On the other hand, 55% of fetal deaths among the unbelted group linked to third-trimester crashes. Therefore, this pattern is probably a result of something different than increased crash risk. These findings

have implications for health providers as well as researchers involved with crash dummy development. For instance, crash dummy testing has mainly focused on the 28–30-week gestational age period for designing the physiological characteristics of a pregnant woman and the fetus [37, 109]. It is important to design dummies representing a few weeks later in gestation to more appropriately target the population that may be at the greatest risk for fetal death. Despite substantial research on the protective value of seat belts, many women still do not wear them during pregnancy. Previous research indicates that the leading reasons for the lack of seat belt use during pregnancy include forgetting, discomfort or inconvenience, no seat belt available, and fear that seat belts may cause injury to the fetus or mother [138]. It is worth noting that some countries exempt pregnant women from seat belt laws, which may be promulgating misconceptions about seat belt use during pregnancy. Many women are simply unaware of the correct usage and positioning of seat belts [134].

Factors associated with low seat belt compliance—younger age, lower education, lower socioeconomic status, seating location (passengers), and longer annual distance traveled—are also important factors during pregnancy [139, 140]. Seat belt use during pregnancy has gone unnoticed in Japan because expectant mothers are exempted from seat belt legislated requirements [141]. Compared with seat belt use before pregnancy, seat belt use during pregnancy was reduced for both drivers and front-seat passengers. This trend is contrary to the finding in California that seat belt compliance significantly increased during pregnancy (79% before pregnancy vs. 86% during pregnancy) [131]. A study in New Mexico, where seat belt use was generally low, found that seat belt use increased from 27 to 42% during pregnancy [138]. If concerns associated with the gestation period dissuade maternal seat belt use, then gestation period would be a major determinant for nonrestraint use during pregnancy. However, a recent study in the United States reported that trimester status has relatively little effect on seat belt use [10].

It is interesting to note that seat belt use was consistently higher among drivers than front-seat passengers despite the discomfort of the steering wheel. Since front-seat passengers are less likely to wear seat belts than drivers among the general population (88.1% for drivers vs. 75.2% for front-seat passengers) [142], it is possible that the same trend would be seen in pregnant women. A large majority of the respondents in studies in the United Kingdom and the United States, where pregnant women are encouraged to continue wearing seat belts, reported that seat belt use is beneficial for both pregnant women and their fetuses [131, 134]. In contrast, only one-third of respondents acknowledged this. Seat belt use was less among pregnant women who knew of the current exemption (Tables 10.7 and 10.8).

Table 10.7 Reported seat belt use before pregnancy and current use among 880 pregnant women in Japan, shown by gestation period [a,b]; results in absolute numbers and %

	<20 weeks		20–29 weeks		30 weeks +	
Location/seat belt use	Before	Current	Before	Current	Before	Current
Driver's seat						
Always	172 (82.3)	129 (62.3)	211 (83.4)	127 (51.4)	229 (78.4)	108 (37.9)
Often	14 (6.7)	22 (10.6)	17 (6.7)	30 (12.1)	31 (10.6)	32 (11.2)
Sometimes	19 (9.1)	34 (16.4)	22 (8.7)	42 (17.0)	29 (9.9)	58 (20.4)
Never	4 (1.9)	22 (10.6)	3 (1.2)	48 (19.4)	3 (1.0)	87 (30.5)
Front passenger's seat						
Always	164 (76.3)	118 (55.1)	190 (72.0)	108 (41.4)	208 (67.3)	89 (29.2)
Often	19 (8.8)	35 (16.4)	24 (9.1)	36 (13.8)	45 (14.6)	26 (8.5)
Sometimes	25 (11.6)	33 (15.4)	41 (15.5)	57 (21.8)	42 (13.6)	81 (26.6)
Never	7 (3.3)	28 (13.1)	9 (3.4)	60 (23.0)	14 (4.5)	109 (35.7)

[a]Total number (in driver's seat) is not equal to the number of pregnant women (with driver's license) due to missing data
[b]Seat belt use before pregnancy was not significantly different across gestation periods, whereas the difference in current use was significant across gestation periods
Reproduced with permission from [143]

None reported that their obstetricians had given this information perhaps because Japanese obstetrics textbooks do not address this issue. In other industrialized countries, obstetricians take an important role in disseminating maternal seat belt use information, and pregnant women who reported receiving this information were more likely to wear seat belts and do so correctly [133, 134]. Daily car users were less likely to wear seat belts despite their longer exposure to the risk of traffic injuries. This suggests that frequent car use may lower risk perception [139, 140]. The limitation of Japanese study [143] is that authors did not examine whether pregnant women wear seat belts correctly, and it is likely that incorrect use is similar to that reported elsewhere [131, 133, 134]. Current recommendations still support the use of three-point restraints (i.e., lap and shoulder belt) for all pregnant women [117]. The lap belt should be placed as low as possible, beneath the bulge of the uterus, and the shoulder belt should lie to the side of the uterus and run between the breasts and over the midportion of the clavicle (Fig. 10.14).

Table 10.8 Proportion of pregnant women who reduced seat belt use after pregnancy, shown by gestation period (%)

Location	20 weeks	20–29 weeks	30 weeks
Driver's seat (%)	25.7	41.1	55.6
Front passenger's seat (%)	27.4	45.2	58.9

Reproduced with permission from [143]

The Airbag

Simulations indicate that for all frontal impacts, it is safest for the pregnant occupant to ride in the passenger seat while wearing a three-point belt and utilizing the frontal airbag when appropriate [144].

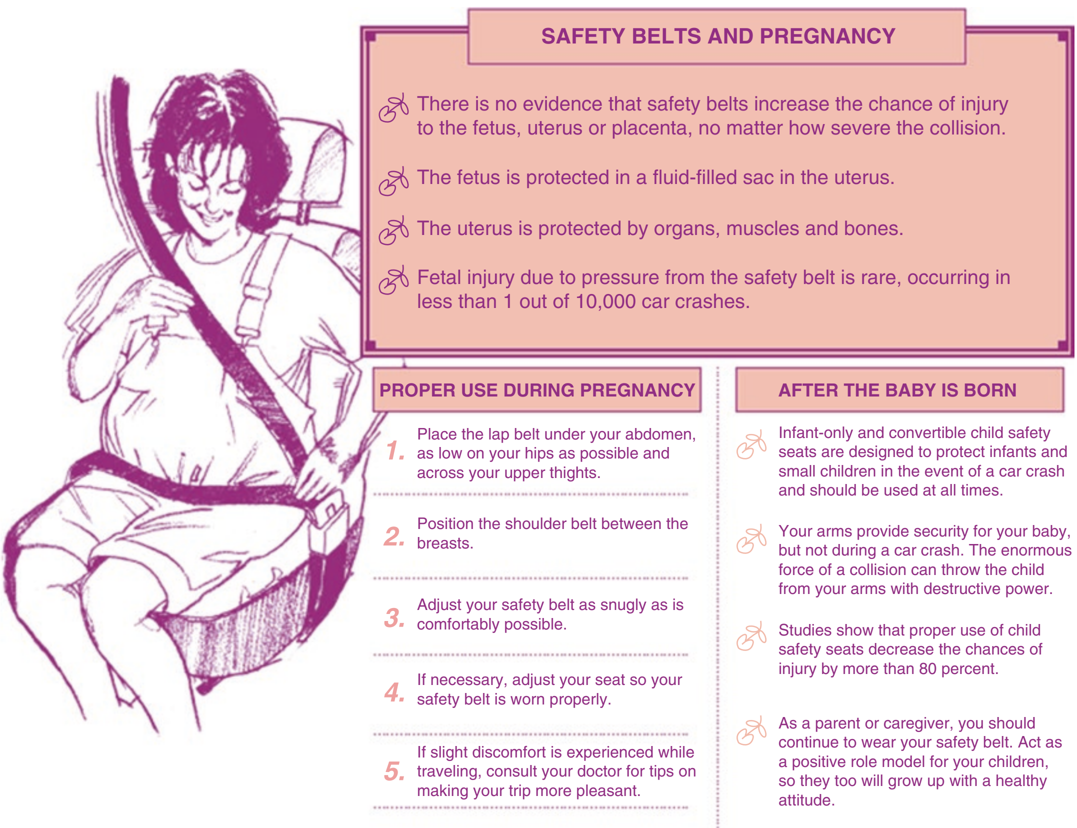

Fig. 10.14 Leaflet about proper position of seat belt in pregnancy. Reproduced with permission from Ohio Department of Public Safety

The airbag is passive safety system of vehicles, which is currently standard equipment. In a crash, the airbag is opened by means of sensors within 30–50 ms and is rapidly filled with gas, usually nitrogen, to softly await the body of passengers and in that way to absorb the inertial force of the body. Airbag for driver and passenger should protect against head injuries and chest in the frontal crash. For the full effect, airbags should work in combination with safety belts that are tied at three points. In the collision of the head and upper body, the airbag must not constitute a strong barrier to maintain constant pressure. The body hitting the bag pushes gas filling through the exhaust openings from the airbag. The basic elements of the airbag are:

- Bag of multilayered composites based on polyamide
- Gas generator
- Contact board with an initiative capsule
- The electronic control unit with a sensor system

To ensure active filling of the airbag, the two sensors are mainly built in a vehicle, in a bumper, and in the divider between the engine parts and space for passengers. The sensor system, a few milliseconds after impact, transmits an electronic signal that activates the initial capsule with approximately 8 g of plastic explosives. The explosion lits the initial mixture in the generator gas, whose combustion releases nitrogen to fill the airbag. The airbag is, after being inflated and having depreciated the impact of the driver, blown out, and the whole cycle takes about 150 ms. Due to the cases when the electronic trigger did not work at the time of the accident, the mechanical activation of the airbag has been introduced. The negative effect of opening the airbag and a loud burst of the strength of 140–160 dB should not pose a threat to human hearing because the impact of vehicle alone into another vehicle or object creates a louder noise.

The biggest imperfection of airbags is their ability to activate when they are simply not expected. Except with failure in the system that may cause the opening of the airbag, there is a risk that the airbag opens in collisions when a vehicle has low speed and the airbag is not needed to absorb the body impact to the steering wheel. In such cases, due to low speed, the body does not come into contact with the interior of the vehicle because of its small inertia forces, but it reinforces the seat belt in the vehicle seat. If the airbag is activated, in such cases, it can cause head and chest injuries, which would not emerge if the airbag is not activated.

Such injuries are especially dangerous because they can cause the death of the fetus. Such phenomena are trying to be solved in a way that airbags do not open up to a certain vehicle speed or up to specific vehicle body deformation. Safety of airbag deployment during pregnancy and in particular during the latter stages and the potential for fetal trauma remain unclear. Some small studies did not found significant maternal or fetal injuries with airbag activation during slow speed collisions [145], while others found a fetal death due to skull fractures with intracranial hemorrhage [146] or placental abruption [147]. Clinicians should be cautious with the conclusion because in some of these case report there were additional risk factors for, for example, intracranial hemorrhage such as maternal anticonvulsant therapy which can increase fetal oxidative degradation of vitamin K, resulting in deficiency and possibly causing neonatal hemorrhage [146].

The European cars are built with two types of airbags:

- 35 L “eurobag”
- 67 L “bull size”

Although the “euro” airbag adds significantly to the safety, measurement results conducted on the dummies in crash tests showed significantly less stress in the critical part of the cervical vertebrae and smaller injuries when using a large “bull-size” airbag. Newer-generation airbags like the French SRP system (System de Retenue Programmee) function in a way that they are programmed to strain safety belts with a pyrotechnic strainer that work in combination with the new generation of airbags. These bags can bend from top to bottom and sideways, which allow regular distribution of tensions in the chest and have a

specially calibrated valve that regulates the throughput power and exhaust of gas. Such combined protection proved to be much more successful than previous ways of functioning, so chest injuries are 70% less.

> Airbags should not be disabled during pregnancy [37, 121].

10.3.2.5 Maternal Pelvic Trauma

In the later stages of pregnancy, retroperitoneal bleeds are a feared and frequent consequence of blunt abdominal trauma [14, 59]. The sudden increase of intra-abdominal pressure leads to rupture of the congested, engorged pelvic venous plexus, fed by the utero-ovarian and infundibulopelvic vessels, into the retroperitoneum [133]. Traumatic retroperitoneal bleeds are often associated with consumptive coagulopathy and have a high incidence of fetal death [148]. Massive substitution of blood products is often required, and a nonoperative approach is initially usually pursued.

The commonest severe fracture reported in pregnancy is a fracture of the pelvis. Fractures of the extremities, ribs, and vertebrae do not necessarily affect pregnancy. Despite the occurrence of pelvic and acetabular fractures among women of childbearing age, literature specifically addressing patients who sustained pelvic or acetabular fractures in pregnancy is scarce. In a recent review, maternal and fetal mortality after pelvic fractures (11 acetabular and 89 pelvic) was 9% and 35%, respectively [149]. Automobile–pedestrian collisions had a statistically higher maternal mortality rate than pregnant women involved in vehicular collisions which had a statistically significant trend toward a higher fetal mortality rate, as compared to falls. Most maternal deaths occurred from associated injuries, in particular from acute hemorrhage [149]. Injury severity influences both maternal and fetal outcomes. Increasing injury severity (minor to moderate to severe) and associated injuries significantly increased both maternal and fetal death rates.

The close association between concomitant abdominal and pelvic injuries and fractures of the acetabulum or pelvis reflects the kinetic injury dissipated with the initial impact. The most common pelvic fractures are through the anterior half of the pelvic ring, usually the horizontal pubic rami [150]. Fracture of the sacrococcygeal joint with ankylosis and encroachment on the capacity of the pelvic outlet may be of obstetric significance [151]. The most common is a fracture of the coccyx and occurs when a pregnant patient falls on her buttocks. The recognition of this fracture is not important for the maternal or fetal outcome but for possible obstruction during labor. A pelvic fracture is often associated with hemorrhage, and the increased vascularity of the pelvis in pregnancy may result in severe bleeding.

Overall, the outcome of patients with pelvic fractures in pregnancy due to blunt trauma correlates with the severity of associated injuries and physiological derangement on admission rather than with characteristics, or the type, of pelvic fracture. The occurrence of pelvic fractures in young patients requires transmission of significant amounts of kinetic energy and should, therefore, be regarded as an index injury mandating a thorough search for other occult visceral injuries.

Fetal Injury

Pelvic trauma in the third trimester of pregnancy should alert the trauma surgeon and obstetrician of direct injuries to the fetus. If the mother survives, fetal loss occurs in the majority of cases because of placental abruption, while direct injury to the fetus in the absence of uterine injury is a relatively infrequent event [152]. Direct injury of the fetus is usually associated with trauma occurring late in pregnancy and most commonly involves fracture of the fetal skull [152]. This is especially likely during the third trimester when the fetal head is engaged low in the pelvis trapped between the anterior pelvic ring and the sacrum. The vast majority of in utero skull fractures have been related to a severe maternal injury involving pelvic fractures [153]. Fetal skull fractures should be regarded as an index injury for severe maternal trauma. Vice versa, multiple pelvic fractures in pregnant women require a thorough sonographic and radiographic examination of the uterus and fetus.

Direct injury to placenta, uterus, or fetus accounted for fetal deaths in 52%, while maternal hemorrhage (with or without maternal death) accounted for 36% of the nonsurviving fetus. These observations are similar to predictors of fetal death after severe trauma in pregnancy in general. Predictors of fetal death in trauma during pregnancy include automobile–pedestrian collisions [33], motorcycle collisions [33], lack of restraints [33], maternal ejection during trauma [33, 51], and increased injury severity score (ISS) [51].

10.3.2.6 Urinary Bladder Rupture

See Chap. 20.

10.3.2.7 Traumatic Rectus Sheath Hematoma

See Chap. 11.

10.3.3 Falls

Falls accounted for more than half of classifiable reported maternal injuries during pregnancy, and about 3% of all mothers reported at least one fall during pregnancy. Falls are also the leading cause of nonfatal injury among women of childbearing age (15–44 years) in the United States, although they account for only 20% of nonfatal injuries among this more general population [154]. Falls may be a more common mechanism of injury during pregnancy, particularly in the second and third trimesters, because of [155]:

- Weight gain
- The shift of the center of gravity to accommodate the expanding uterus
- Increased joint mobility

Increased levels of relaxin result in softer ligaments, cartilage, and cervix allowing the tissues to spread during delivery. The pubis symphysis—cartilage joining the pubic bones—and sacroiliac joint, where the hips attach to the spine, become unstable during pregnancy to aid delivery.

The occurrence of falls becomes more likely as pregnancy progresses, with nearly 43% of reported falls occurring during the third trimester [156, 157]. Although extensive clinical guidelines (*American Geriatrics Society*, *British Geriatrics Society*) exist for physician counseling about the importance of fall prevention in the elderly, clinical guidelines for counseling about fall prevention for pregnant women are limited to warnings against strenuous physical activities with high risk for falls, such as horseback riding and skiing. In the injury descriptions, falls during pregnancy most often occurred during normal daily activities.

10.3.4 Social/Domestic Violence

10.3.4.1 Introduction

There are two types of social violence: homicide and suicide. Such violence during pregnancy has been identified as a risk factor for homicide by an intimate partner [158]. Suicide may represent the only way out of repeated episodes of domestic violence [159]. Domestic violence is carried out by an intimate partner or family members. Unwanted pregnancy, sometimes as a consequence of sexual abuse, may lead to suicide under social circumstances stigmatizing women who have a pregnancy out of wedlock. It is especially evident in societies where access to family planning is limited and access to abortion is restricted. The neglect of the contribution of violent deaths to maternal mortality seems to be due in part to the misconception that homicide, suicide, and accidents occur only by chance during pregnancy. Because many women seek medical attention only when they become pregnant, health-care providers of pregnant women play a crucial role in discriminating women who are abused.

Deaths during pregnancy or the puerperium due to suicide, homicide, and accidents were initially excluded in the definition of maternal death and later classified as "pregnancy-related" by the tenth Revision of the International Classification of Diseases. An understanding of the relationship between violence in pregnancy and the adverse maternal outcome can have important clinical and public health implications for successful safe motherhood initiatives.

10.3.4.2 Incidence

Because the woman has her unborn child's safety in mind, she may be more motivated to seek assistance, and she may speak more freely during pregnancy. The reported rates of abuse vary significantly, 5.4–27.7% [160–162]. This reflects both a genuine diversity in the occurrence of violence and in definitions of abuse used by researchers. The prevalence of interpersonal violence during pregnancy ranged from approximately 2.0% in Australia, Cambodia, Denmark, and the Philippines to 13.5% in Uganda among ever-pregnant, ever-partnered women; half of the surveys estimated prevalence to be 3.9–8.7%. Prevalence appeared to be higher in African and Latin American countries relative to the European and Asian countries surveyed. In most settings, prevalence was relatively constant in the younger age groups (15–35 years) and then appeared to decline very slightly after age 35 [163]. As many as 20.6% of pregnant teenagers and 14.2% of pregnant adult women were physically abused during pregnancy [164]. Interpersonal violence has been emphasized as an etiology of trauma only during the past few decades. Sexual or physical abuse occurs in up to 17–32% of pregnancies, and 60–75% of those abused reported multiple episodes of abuse with (repeated) hospitalizations [25, 165, 166]. This scenario can be repeated in subsequent pregnancies [166]. Abuse often begins or escalates during pregnancy or the immediate postpartum period. Most often the abuser is known to the patient, frequently her husband or partner.

10.3.4.3 Risk Factors

Young women (<25 years) comprised 59% of maternal deaths due to injuries, whereas injuries constitute 47% among all maternal deaths in Maputo [167]. A study in Bangladesh showed that pregnant or puerperal women aged between 15 and 19 years were nearly three times more likely to die from injuries than nonpregnant and nonpuerperal women of the same age and were also at significantly higher risk than older women [168].

Several studies found strong associations between violence and substance abuse. Victims of violence were significantly more likely to smoke, to drink alcohol, and to use illegal drugs both before and during pregnancy [169, 170].

10.3.4.4 Clinical Presentation and Diagnosis

Domestic violence occurs in up to 25% of pregnant women [42, 43], but physicians detect only 4–10% [25]. Regardless of the apparent severity of injury in blunt trauma, all pregnant women should be evaluated in a medical setting [4]. It is important for physicians to screen all patients for domestic violence and to be familiar with the community resources for helping patients who experience domestic abuse [42]. As with any trauma patient, the entire body needs to be examined, looking for hidden injuries under clothes, makeup, jewelry, or wigs. Injuries range from cuts, bruises, and black eyes to miscarriage, bony injuries, splenic and liver trauma, partial loss of hearing or vision, and scars from burn or knife wounds. Injuries to the breast, chest, and abdomen are more common in battered women, as is the presence of multiple old and current injuries. Defensive injuries are common. For example, fractures, dislocations, and contusions of the wrist and lower arms result from attempts to fend off blows to the chest or face. Injuries inconsistent with the patient's explanation of the mechanism of injury should also raise suspicion of abuse. The presence of these patterns of injury should raise concern about abuse during evaluation in the emergency room (Table 10.9).

Table 10.9 Warning signs of domestic abuse

Mixture of old and new injuries
Characteristic injuries (multiple soft tissue injuries, fingernail scratches, cigarette and rope burns, areas usually covered by clothes—Breast, chest, abdomen, genitals)
History of prior domestic abuse
Isolating behavior of partner
Behavior of patient: Depressed, poor eye contact, fearful, withdrawn
Pregnant patient: Trauma to breast and abdomen; no prenatal care; unexplained spontaneous abortion, miscarriage, or spontaneous labor
Family income below $10,000/year

Reproduced with permission from [42]

10.3.4.5 Prognosis

Fetal Outcome

It is possible that minor trauma during pregnancy may lead to the subclinical chronic placental disruption that persists during pregnancy, which may cause an increase in the risk for induced abortion, acute placental abruption, preterm labor, preterm premature rupture of the membranes, and placental insufficiency that restricts fetal growth and lower Apgar score [171].

Around 1/3 of studies reported a positive association between intimate partner violence and low birth weight or preterm birth [172–174]. Rates of low birth weight among battered women were 1.5–2.5 times higher [172–174] than those among nonbattered women, and rates of preterm birth were 2.5–4 times higher [172–174]. Others lacked sufficient power to address most pregnancy outcomes [175, 176]. Many studies have reported increased rates of low birth weight, reduction in mean birth weight, or preterm labor in bivariate analyses, but the associations became nonsignificant when adjusted for use of tobacco and other substances [177, 178].

Fetal loss can occur even when the mother has incurred no abdominal injuries [34, 46]. Pregnant patient presenting with blunt trauma not from traffic should be examined in detail for the signs of older trauma which could lead to chronic violence.

10.3.5 Obstetric Complications

The data lack patient follow-up with the result that little is known or tracked about nonfatal fetal crash outcomes. MVAs are probably a larger threat to fetuses than to infants due to increased crash involvement, increased vulnerability due to dependence on placental circulation for survival, vulnerability to sensitive developmental periods of risk, and perhaps comparatively less protection from the in utero environment than infants receive from safety seats.

There are two principal mechanisms of obstetric trauma: direct injury and deceleration injury. Both types have some specific patterns of obstetric trauma, while some, such as traumatic placental abruption, are common for both types.

10.3.5.1 Traumatic Placental Abruption

Incidence

The incidence of traumatic placental abruption is approximately 5% [7, 59, 135]. Clinically evident placental abruption occurs in up to 40–50% of severe blunt abdominal trauma and 1–6% of minor trauma with direct uterine trauma [7, 137, 179]. The correlation between seat belt sign in pregnancy and traumatic placental abruption is unknown.

Pathophysiology

The mechanism of placental abruption resulting from trauma is based on the fundamental differences in tissue characteristics between the uterus and the placenta. The uterus consists of a significant proportion of elastic fibers, whereas the placenta is largely devoid of elastic fibers. Thus, when an external deforming force is applied to the uterus, its inherent plasticity allows deformation. At the same time, the placenta cannot undergo similar deformation, and a shearing effect is created at the uteroplacental interface. It is also thought that concomitant increases in amniotic fluid pressures propagate this shearing effect, further separating the placenta from the underlying decidua (Fig. 10.15). Experiments have been conducted on pregnant baboons, which were subjected to decelerative forces (~20G) typical of MVAs [180]. Such forces produce very high intrauterine pressures (~550 mmHg).

Because most blunt abdominal trauma occurs to the anterior uterine wall, one would expect that if the mechanism of separation were just displacement from the striking object, the risk of placental abruption would be greater when the placental location is anterior. However, the pathophysiological mechanism of separation just described does not explain the finding that an anterior placental location does not appear to be a risk factor for placental abruption resulting from trauma [59]. Two alternative possibilities should be considered. Firstly, the contained mass within

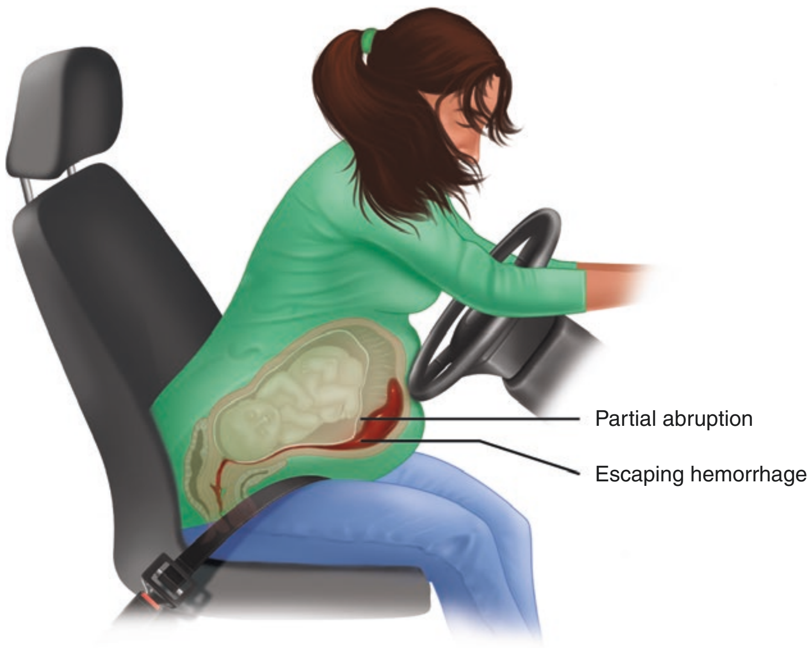

Fig. 10.15 Acute deceleration injury occurs when the elastic uterus meets the steering wheel. As the uterus stretches, the inelastic placenta shears from the decidua basalis [155]

the amniotic fluid (i.e., the fetus) can either strike the placenta in any location and thus create a potential shear or, alternatively, pull the placenta by transmitting force via the umbilical cord. A second possibility that could explain the lack of importance of placental location on the likelihood of placental abruption is that traumatic deformation may set up a fluid wave within the uterus. In this case, a force striking the anterior uterine wall would cause elongation and narrowing of the uterus as the contained amniotic fluid is noncompressible. The fluid wave would then "rebound" and expand horizontally causing a shortening and widening of the uterus. Again, because of the fundamental tissue differences between the uterus and placenta, a shearing effect of this interface could occur completely independent of placental location [50, 84]. Placental abruption risk is independent of whether the placental location is anterior or posterior.

Compression of the vena cava has been shown to cause placental abruption in animal experiments during the 1950s [181, 182]. In view of this, it was suggested that when placental abruption does not occur immediately after trauma, it may result from placing an injured patient in the supine position [48].

Abruption was found to be more likely if vehicle speed exceeded 50 km/h [183].

Clinical Presentation

Traumatic placental abruption may occur even when there are few other signs of trauma. It almost invariably results in termination of pregnancy within 48 h of the traumatic episode [150, 184]. If the area of placental separation is large enough to compromise fetal oxygenation, labor or fetal death will occur within 48 h, and if death or labor does not occur within 48 h, harm to the fetus from the placental separation is unlikely [184].

Clinical findings may include vaginal bleeding, abdominal cramps, uterine tenderness, amniotic fluid leakage, and maternal hypovolemia out of proportion to visible bleeding. Only 35% of clinically significant placental abruptions had vaginal bleeding [77]; remaining hematomas are confined to the uterus and do not manifest as vaginal bleeding. Up to 2000 mL of blood can accumulate in the uterus, and this can be a cause of maternal shock, but frequently the shock in patients with placental abruption is out of proportion to the observed blood loss and is a result of profound hypovolemia from additional injuries. In a patient with intra-

uterine hemorrhage, the uterus may be larger than normal for gestational age.

Principal maternal complications associated with placental abruption are:

1. Hemorrhagic shock resulting from acute whole blood loss and resultant contraction of the intravascular compartment.
2. Generalized coagulopathy occurring because of active consumption of clotting factors within the vascular tree and consequent secondary fibrinolysis.
3. Ischemic necrosis of distant organs. The organs most frequently involved are the kidneys and the anterior pituitary gland. Acute renal failure is a serious complication and may lead to maternal death.
4. Preterm PROM resulting from decidual hemorrhage.

Diagnosis

Commonly used coagulation tests, such as PT and partial thromboplastin time, are insensitive indicators of DIC; more than 50% of clotting factors must be consumed before these test results become abnormal. Fibrinogen levels are sensitive indicators of DIC on serial testing. A fibrinogen concentration of less than 200 mg/dL in a pregnant patient is abnormal. Clinical evidence of bleeding may appear when the value is less than 100 mg/dL. The platelet count decreases in concert with fibrinogen levels, but in most cases, there is a greater decrease in the fibrinogen level than in the platelet count. The most sensitive laboratory test for diagnosis of coagulopathy related to abruption may be the determination of fibrin–fibrinogen degradation products by a variety of techniques, including D-dimer assays [185]. Despite being frequently elevated in cases of placental abruption, most studies failed to demonstrate clinical usefulness as a screening test [36, 185]. Although placental abruption is frequently found in association with FMH, screening for fetal blood cells in the maternal circulation with Kleihauer–Betke tests has a low specificity and is not recommended [13, 121, 186].

Diagnostic imaging modalities are described in the Sect. 10.3.6.

Treatment

Fetal compromise is present in over 60% of placental abruptions with a live fetus, and an immediate CS is indicated (see Chap. 23).

Prognosis

Over 70% of fetal losses following blunt abdominal trauma result from placental abruption [49, 50, 84, 179, 187]. The overall fetal mortality with placental abruption is 54% [15]. If maternal shock occurs, fetal mortality approaches 80%.

10.3.5.2 Placental Tear

History and Incidence

Traumatic laceration (rupture, “fracture”) of the placenta following blunt abdominal trauma is even more infrequent than placental abruption. The first case published was by VanSante in 1942 when he reported a case in which blunt trauma to the maternal abdomen resulting from a fall off a stepladder was followed by spontaneous delivery of a stillborn infant and a placenta showing a clean laceration through both the fetal and the maternal surface at the area of insertion of the umbilical cord [188]. In 1969, Peyser and Toaff reported a similar case following an MVA in which a radial tear involved the whole thickness of the placenta; the fetus subsequently bled to death in utero [189]. The uterus, umbilical cord, and fetus were completely intact in all published cases [190].

Pathophysiology

There are two mechanisms of placental injury. The placental injury may be mediated by either a countercoup or a direct force depending on the location of placental implantation and the direction of abdominal injury/deceleration. Following the disruption of the placental circulation, the fetus bleeds to death in utero.

Countercoup Mechanism

If the placenta is implanted posteriorly in the uterus and deceleration starts, a countercoup mechanism similar to that in closed-head injuries occurs. Although the initial decelerative force is applied to the anterior abdominal and uterine walls, the incompressible amniotic fluid immedi-

ately anterior to the fetus would have retarded the forward movement of the fetus. The sudden anterior force to the uterus momentarily causes the posterior uterine wall and the placenta to move away from the fetus, the result being a "vacuum" between the fetus and the posterior wall. When the anterior decelerative force was no longer applied to the uterus, the posterior wall would have stopped moving, and the vacuum would have caused the fetus to be projected against the placenta on the posterior uterine wall. In this situation, the amniotic fluid, instead of acting as a buffer for the fetus, is operating as a vehicle for fetal movement, allowing sufficient mobility for a countercoup injury of the placenta. This is analogous to the injury of the occipital region of the brain following a frontal blow when the cerebrospinal fluid acts as the vehicle for countercoup movement of the brain.

Direct Placental Injury

When the placenta is implanted anteriorly in the uterus, the initial decelerative force applied to the anterior uterine wall causes the fetus to be propelled forward. The amniotic fluid, though incompressible, allows the fetus to travel forward with sufficient momentum to apply a sudden force to the surface of the placenta implanted on the anterior uterine wall, causing a "bursting" or irregular laceration of the fetal surface of the placenta (Fig. 10.16).

10.3.5.3 Preterm Labor

See Chap. 23.

10.3.5.4 Fetal Injury

Direct Fetal Injury

Direct fetal injuries and fractures complicate less than 1% of severe blunt abdominal trauma in pregnant women, since the maternal soft tissue, uterus, and amniotic fluid absorb energy and diminish the force delivered to the fetus. Most cases, with severe injuries, occur during late pregnancy [7, 84]. Cranial injuries are the most frequently reported category of direct fetal injury after blunt abdominal trauma. Fetal brain and skull injuries may be more common in cases with fetal head engagement in which maternal pelvic fractures occur [92, 191]. Deceleration injury to the unengaged fetal head may also occur [7, 84]. Isolated fractures of the mandible, the clavicle, the vertebrae, and all the long bones have been reported [48]. In these direct injuries either the maternal abdominal wall is struck by a blunt instrument or the maternal abdomen strikes the car's dashboard, steering wheel, or another area. Such injuries may not be diagnosed at the time of the accident, and the pregnancy may well continue to term in the absence of concomitant placental or uterine injuries. Intrauterine fetal fractures may spontaneously heal in utero, as evidenced by callus formation at the fracture site [48].

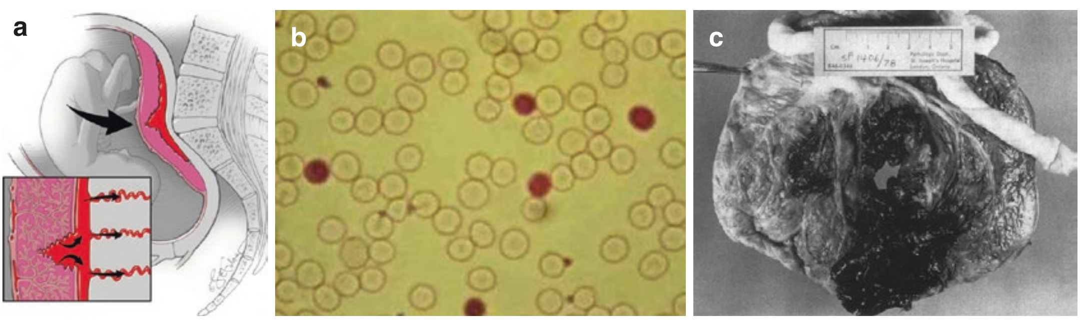

Fig. 10.16 (**a**) Mechanism of placental tear or "fracture" caused by a deformation–reformation injury. Placental abruption is seen as blood collecting in the retroplacental space. (*Inset*) From here, the blood can be forced into placental bed venules and enter maternal circulation [155]. (**b**) Such maternofetal hemorrhage may be identified with Kleihauer–Betke testing. Peripheral smear of maternal blood. The dark cells that constituted 4.5% of red blood cells are fetal in origin, whereas the empty cells are maternal [155]. (**c**) Approximately 3 cm from the insertion of the umbilical cord was an elliptical laceration of the placenta through both the fetal and the maternal surfaces (6.5 × 2.8 cm). The cotyledons were intact, but there were masses of clot adherent to the fetal surface. Microscopically the placenta and the umbilical cord were normal. Reproduced with permission from [190]

Indirect Injury of the Fetal Viscera

Indirect injury of the fetal viscera—that is, injury in the absence of external evidence—has been reported, but one can only speculate on the mechanism of injury. Connor and Curran reported a case in which the fetus suffered hepatic, renal, and adrenal contusions and hemorrhage without showing external evidence of trauma [192]. They suggested that the injury was due to rapid compression and impact of the organs during deceleration, but whether it resulted from a countercoup effect within their attachments or was secondary to a shearing force within the organs could only be conjectured [193].

10.3.5.5 Traumatic Uterine Rupture

Uterine rupture can be spontaneous (see Chap. 16) or traumatic—a rare complication of blunt abdominal trauma, complicating about 0.6% of traumatic events during pregnancy [7]. Traumatic uterine rupture is practically unique to pregnancy, and one of the first cases found was by Lazard and Kliman from 1936 [194]. The first case with fetal mortality, in conjunction with uterine rupture, was reported in 1950 by Elias [195]. Lazard and Kliman proposed a classification of traumatic uterine rupture:

- *Complete*, through the entire uterine wall, with complete or partial extrusion of the uterine contents into the abdominal cavity
- *Incomplete*, where the rupture is not through the entire uterine wall. As to location, the tear may be in the upper or in the lower uterine segment, usually the upper when due to external trauma

Incidence

Up to and including 1929, Estor and Pueck (referred to by Jaroschka, Medizinische Klinik, 1929) collected 40 cases. Additional cases in the 1930s were collected by Orthner [196], Lazard and Kliman [194], and Ruder and Moore [197]. During last 50 years, the increase of motor vehicle use resulted in the increase of blunt abdominal trauma resulting in traumatic uterine rupture [198–200]. Over 100 cases of traumatic rupture of the pregnant uterus have been reported up to 1975, with only three [195, 201, 202] with the avulsion of the uterus. The overall incidence of all-cause uterine rupture significantly varies (see Chap. 16). In patients hospitalized for assault during pregnancy, the incidence of uterine rupture reached 0.71% with an odds ratio of 46 compared with women with no history of assault [203].

Etiopathogenesis

Traumatic Uterine Rupture

While a trauma of sufficient force may cause a rupture in a healthy uterus, the presence of a weakened point caused by preceding disease, such as hyaline degeneration of muscle fibers resulting from multiparity, previous curettages, placenta previa, intramural fibroids, etc., would undoubtedly increase the probability of rupture resulting from external violence. Orthner gives the following explanation of the mechanics of the injury [196]: as to whether the blow or the resultant fall is the principal factor, one can assume that whichever is of the greater intensity is the chief factor, i.e., with a slight blow and a fall from a great height, the latter is the main factor; with a severe blow and a short fall to the floor, the blow in all probability is to blame. It is not possible, as a rule, to determine the kind and direction of the force from the location of the uterine rupture, as this usually occurs by countercoup.

The rupture is always the result of a sudden increase of the intrauterine pressure, caused by the sudden compression of the abdominal contents. In accordance with the laws of hydrodynamics, this pressure spreads equally in all directions in the uterine cavity filled with amniotic fluid. The tear occurs at the weakest point of the uterine wall. At the end of pregnancy, that point is at the fundus [194], which, moreover, lacks the protection of the bony pelvis. In many

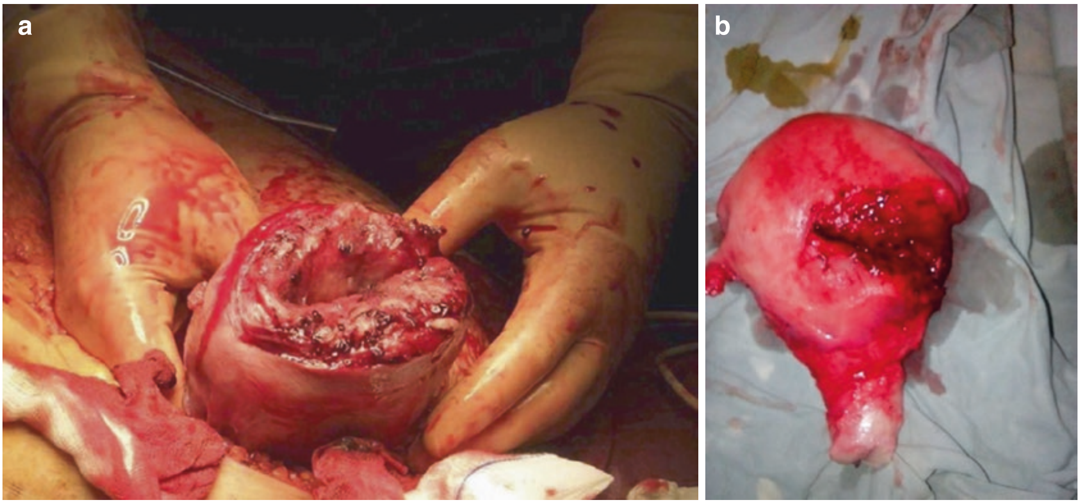

Fig. 10.17 Ruptured uterus. (**a**) The most common location is uterine fundus (Reproduced with permission from [207]), but other locations (**b**) can also be found depending on the mechanism of trauma. Reproduced from [204] under the CC Attribution License

cases, it appears that the placental site is especially weak because of the increased vascularity. It is not known whether uterine scar from previous CS indicated due to myomectomies is prone to rupture. The site of rupture bears a direct relationship to the site where direct traumatic or countercoup forces are applied mostly involving the uterine fundus (Fig. 10.17a), although other locations and degrees of uterine rupture from other causes have also been reported (Fig. 10.17b), [7, 84, 204, 205]. This is because amniotic fluid transmits high pressures efficiently; "blast injuries" can follow blunt trauma, resulting in rupture of the uterine fundus in 75% of cases. During the first trimester, the uterus is protected by the pelvis, and it is likely that uterine avulsion can occur solely in combination with a pelvic ring fracture [202]. There are even cases with the seat belt as proposed etiological factor [206].

The extent of the uterine rupture can be variable. Such an injury may result in serosal hemorrhage or abrasions; avulsion of the uterine vasculature with hemorrhage; complete disruption of the myometrial wall with extrusion of the fetus, placenta, or umbilical cord into the abdominal cavity; or complete uterine avulsion [121].

Fetal Injury

Traumatic uterine rupture is commonly associated with direct fetal injury. Normally, uterine blood flow increases ten times—from the non-gravid rate of 60 cm^3/min up to 600 cm^3/min at term [7]. Acute loss of blood volume is compensated in part by an increase in uterine vascular resistance and decreased uterine blood flow [51]. Hemodynamic stability of the mother, therefore, is maintained at the expense of uterine blood flow, putting the fetus at risk [35, 152].

Diagnosis

The diagnostic modalities used to depend on the severity of the maternal injury. In severe abdominal trauma with uterine rupture, the fetus can be palpated in the abdomen outside the uterus. Or this condition can be diagnosed by abdominal CT scan (Fig. 10.18). In extreme situations, on plain (abdominal) X-rays, the fetus can be found in abnormal positions, such as on mother's thigh (Fig. 10.19).

Coutts explained two possible mechanisms [208]:

1. The bus struck the woman on her left side, throwing her on the ground, and went over her; the pressure of the tires and counterpressure of the ground ruptured the uterus, and the pressure continuing downward and to the

Fig. 10.18 Abdominal CT scan showing fetus in the abdominal cavity and hemoperitoneum, findings consistent with complete uterine rupture. Reproduced with permission from [207]

Fig. 10.19 A vertical incision was made on the upper anterior surface of the right thigh, extending up to the groin, and the fetus was found lying just under cover of the skin and superficial fat. Reproduced with permission from [208]

right forced the fetus down into the thigh (the fetus was about 23 weeks old, so the uterus would be above the brim and nearing the level of the umbilicus).

2. The original blow and pressure were on the right side and stripped the skin and superficial fascia of the thigh, detaching the inguinal ligament from its attachments and the abdominal muscles from the anterior third of the iliac crest; the same force, continuing to act, tore the peritoneum and ruptured the uterus. On release of the pressure, the uterus rebounded forward and squeezed out the fetus, which passed out under the skin of the right thigh along the line of least resistance.

Clinical Presentation

Clinical presentation can vary from subtle findings (e.g., uterine tenderness, nonreassuring fetal heart rate patterns) to a rapid onset of maternal hypovolemic shock. The classic description of uterine rupture includes the following: severe uterine pain and tenderness, profound shock, palpation of fetal parts outside the uterus, and vaginal bleeding. The examination can reveal (moderately) distended abdomen with suprapubic tenderness and guarding. The uterus can be difficult to palpate. Pelvic examination confirms normal external genitalia and closed firm cervix. Fullness in the pouch of Douglas can be found with the examining finger stained with blood. The presence of maternal hypotension is a late and ominous sign. These complex findings, however, often are not present [209–211]. Consequently, the diagnosis is often delayed or not considered at all. Hemodynamic stability of the mother is maintained at the expense of uterine blood flow, putting the fetus at risk [35, 152]. As a consequence, fetal distress may be the first indicator of unsuspected maternal hemorrhage.

Treatment

The diagnosis of uterine rupture warrants immediate surgical intervention. As to therapeutic procedure, much depends on the location of the rupture and the degree of injury (Table 10.10).

Total abdominal hysterectomy is considered the operative intervention of choice, although

Table 10.10 (Pregnant) uterus injury scale

Grade[a]	Description of injury	AIS-90
I	Contusion or hematoma (without placental abruption)	2
II	Superficial laceration (<1 cm) or partial placental abruption <25%	3
III	Deep laceration (≥1 cm) in second trimester or placental abruption 25–50% Deep laceration (≥1 cm) in third trimester	3 4
IV	Laceration involving uterine artery Deep laceration (≥1 cm) with >50% placental abruption	4 4
V	Uterine rupture • 2nd trimester • 3rd trimester	 4 5
	Complete placental abruption	4–5

[a]Advance one grade for multiple injuries up to grade III
Reproduced with permission from [212]

subtotal hysterectomy or simple suture repair may be reasonable alternatives [209, 211]. If it occurs in the fundus, a repair of the laceration is quick and is done with less shock. If the tear is located in the lower segment, transverse hysterectomy is indicated. Palliative measures must be considered and might be lifesaving, such as the application of the Momberg belt or clamping the uterine arteries through the cervix until the patient can be relieved of shock and prepared for surgery.

Prognosis

Uterine rupture tends to occur only in the most serious accidents involving direct abdominal trauma. This event can be catastrophic for both the mother and her unborn fetus, especially when there is a delay in the diagnosis, since initial symptoms may be variable. With traumatic rupture, fetal mortality approaches 100% and maternal mortality close to 10% with most maternal deaths due to concurrent injuries [7, 107, 213]. At first glance, it is striking that most of the patients reported have survived. However, a reason for the survival is to be found in the fact that the blood vessels constrict and thus the bleeding rapidly diminishes or even stops entirely. The uterine contents (the placenta, the amniotic sac, etc.) are immediately emptied into the abdominal cavity, whereupon the uterus contracts as it would following CS. Since the blood supply at the midline (where the rupture usually occurs) is scanty, these contractions of the uterine muscle practically stop the bleeding. This consideration suggests that in cases where the placenta is inserted more toward the parametrial region, where the contractibility is less and the blood vessels are much larger, the trauma would result in fatal exsanguination.

10.3.5.6 Fetal–Maternal Hemorrhage

Incidence and Risk Factors

FMH is a physiological event by the transmittance of low blood volumes between mother and fetus and thus remains clinically insignificant and undetected. Severe FMH has been described as a fetal blood loss of more than 30 mL [214]. The incidence of all-cause clinically significant FMH is estimated between 1/3000 and 1/10,000 women [214]. However, there is a high number of cases that remain unreported [215]. More important for the determination of the severity is the time frame in which blood is hemorrhaged, as well as fetal and potential maternal mechanisms to counteract cardiovascular distress. In this context, the gestational age might also play an important role [216].

FMH is the transplacental passage of fetal cells into the maternal circulation and is a unique complication of pregnancy. The reported incidence is 8–30% in traumatized pregnant women, compared with 2–8% for nontraumatized mothers, and the volume of transfused blood is also greater in injured women [41, 59, 77, 84]. Anterior placental location and uterine tenderness have been associated with an increased risk of FMH.

> Neither the severity of maternal injury nor the presence of uterine activity is predictive of FMH [7, 50, 59].

Clinical Presentation

Due to its rarity, it is probable that even the experienced clinician will seldom encounter FMH. Therefore, it is important to detect the symptoms and signs of potential FMH early to take appropriate action to prevent further damage to fetus and mother. Symptoms can be neonatal anemia, followed by decreased or absent fetal movement as well as stillbirth. In addition hydrops fetalis, pathological CTG pattern, and intrauterine growth restriction were mentioned as potential signs [214].

Diagnosis

When FMH is suspected, the detection of fetal cells in the maternal blood stream is necessary for confirmation. The most widely used test remains the *Kleihauer–Betke test*. Fetal red blood cells containing fetal hemoglobin are identified by erythrosine staining; maternal red blood cells remain unstained (ghost cells). It is semiquantitative test, an acid elution assay which may alert the obstetrician to a serious hazard for the fetus even in Rh+ women.

> Kleihauer–Betke test should be considered for every woman regardless of their Rh status in order to determine the Rh immune globulin dose necessary to be administered to women who are Rh- and suffered a massive transfusion [7, 41, 49, 50, 59, 77]. However, a positive test alone did not necessarily indicate FMH in low-risk pregnant trauma patients [186].

The amount of FMH sufficient to sensitize Rh- mothers is far below the level detected by most laboratories. The technician must count 10,000 erythrocytes and assess the percentage of fetal cells, making this method very labor-intensive and error-susceptible procedure. Studies have shown a tendency to underestimate fetal cells, as they contain increasing amounts of adult hemoglobin at term [214], as well as an overestimation in cases of hemoglobinopathies (such as sickle cell anemia). The positive Kleihauer–Betke test is present in 8–30.6% indicating FMH [7, 41, 77]. This difference in the FMH rate is likely due to different inclusion criteria (noncatastrophic vs. catastrophic trauma) [166]. Until more sensitive diagnostic tools for detection of placental abruption and subsequent FMH are available, continued use of the commonly available screening tests for all pregnant women who have abdominal trauma is recommended.

Using the *rosette test* a sample of maternal blood is incubated with Rho(D) immune globulin, which will bind to any fetal Rh-positive red blood cells if present. Upon addition of enzyme-treated cDE indicator cells, the presence of Rh-positive fetal blood causes rosetting, which can be seen by light microscopy. In a positive test, it is recommended that a Kleihauer–Betke test should be performed to confirm and quantify any positive rosette tests.

Another method used is flow cytometry. Fetal hemoglobin is tagged with a fluorescent antibody and subsequently quantified in an automated way, making it both less labor-intensive and more objective. The method has additional potential applications for the study of HbF levels or frequency of adult red cells with low levels of HbF (F cells) in individuals with hemoglobinopathies [217]. However, not every hospital has the necessary infrastructure, and samples sent to centralized laboratories might get altered by transportation.

A suspected case of FMH requires an immediate detection. There are formulas to assess the estimated total volume of hemorrhaged fetal blood [218], but the sensitivity of these formulas is limited by the fact that total fetal and maternal blood volume is estimated and the rate at which blood volume loss occurred cannot be determined.

Treatment

Both mother and fetus can be and should be treated. The volume of fetal blood loss after trauma varies: 5–40 mL—this can represent up to 34% of fetal blood volume. As little as 1 mL of Rh+ blood can sensitize 70% of Rh− women [41, 219]. Therefore, all Rh− mothers who present with a history of abdominal trauma should receive a prophylactic dose of Rh immune globulin. In Rh− pregnant women, administration of Rho(D) immune globulin is unnecessary after insignificant superficial injury confined to an extremity. After any other trauma, the immune globulin should be administered within 72 h to all Rh− women, including those who are at less than 12 weeks of gestation and those who have minimal injuries [121]. The Kleihauer–Betke test can

be helpful in Rh− mothers to roughly quantify the volume of FMH. All Rh− patients with a positive test should be treated with Rh immune globulin (300 μg initially and a positive test should be repeated in 24–48 h to investigate continuing FMH). One dose (300 μg) of the immune globulin is sufficient in 90% of cases of FMH because most FMHs are less than 30 mL of blood [121]. An additional dose of 300 μg for each 30 mL of estimated FMH is administered to reduce the risk of isoimmunization. Therefore, Kleihauer–Betke test is unnecessary [36, 46, 121, 220], unless an FMH needs to be quantified for accurate dosing of the immune globulin [13, 121].

When severe FMH is detected in a vital fetus with cardiovascular distress, there are two options of treatment: delivery or prolongation of pregnancy (Fig. 10.20). The latter will include intrauterine blood transfusion (IUT) and the application of steroids at a gestational age of 23 weeks and 5/7 days for lung maturation. Fetal transfusions are performed up to 35 weeks of gestation, with delivery anticipated at 37–38 weeks. If the pregnancy is near term,

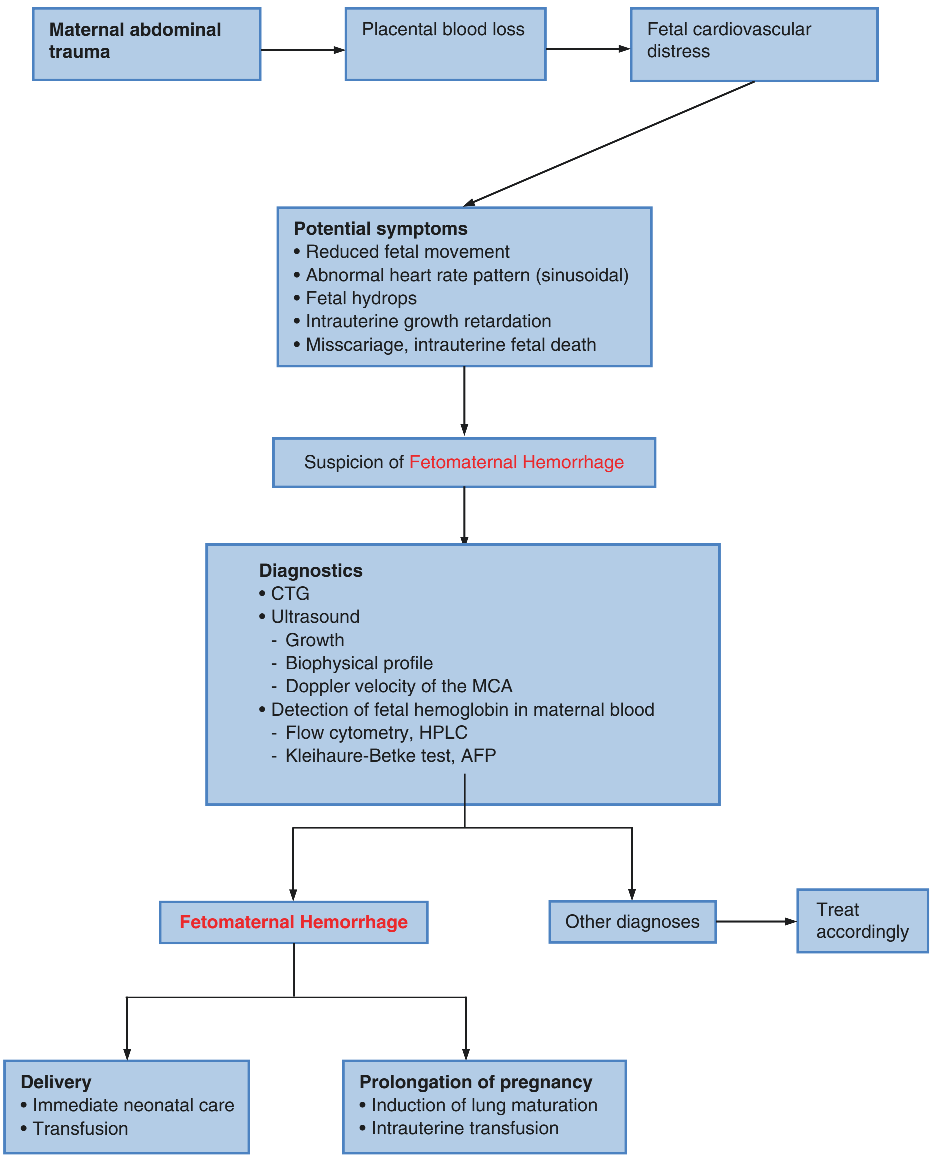

Fig. 10.20 Complete flow sheet of FMH. Modified with permission from [216]

emergency delivery and immediate blood transfusion are the treatment of choice, particularly if the transfer to a unit with IUT facility would be too time-consuming. IUT treatment after 32 weeks of gestation might be safer than procedures performed in early gestation and may prolong pregnancy until safe term and improve outcome [221, 222]. However, every IUT carries a risk of procedure-related asphyxia, especially in a compromised fetus.

Prognosis

Fetal complications of all-cause FMH include fetal/neonatal anemia, fetal tachycardia/arrhythmia, and intrauterine fetal death due to hypovolemia and cardiac failure [7]. Therefore, investigation of unexplained fetal death should include a Kleihauer–Betke test performed on the mother [58]. It can also be performed on vaginal blood in cases of antepartum hemorrhage to identify a fetal bleed [223, 224].

> A Kleihauer–Betke test is not predictive of fetal outcome [13, 15, 46, 59, 121, 225].

The incidence of FMH adverse outcome is high (31–46%), most of them being perinatal death, while morbidity is mostly neurological in a form of periventricular leukomalacia [226, 227].

Maternal complications of FMH include rhesus (Rh) sensitization in the mother. Although the incidence of FMH is four times higher in pregnant women with trauma compared to pregnant women without trauma and the amount of FMH is four times as large on average in cases of trauma, these two patient groups have similar outcomes [59].

10.3.5.7 Amniotic Fluid Embolism

Incidence

Amniotic fluid embolism was first described by Meyer in 1926 and established as a clinical entity by Steiner in 1941 [228]. The first published case after blunt abdominal trauma in pregnancy is by Olcott in 1973 [229]. The overall incidence has been reported in the range of 1/8000–1/80,000 live births [229]. There are only a few published cases of amniotic fluid embolism after blunt (abdominal) trauma [229–233].

Risk Factors

Commonly it occurs during labor and delivery or immediately postpartum. It has also been described following CS, amniocentesis, or therapeutic abortions. Very rarely it occurs in the late postpartum period or in a nonlaboring woman [234]. Blunt abdominal trauma during pregnancy is proposed to be one of the risk factors. All cases have occurred in car accidents in a healthy woman during the third-trimester pregnancy [233].

Pathophysiology

The pathophysiology, in general, is still not revealed. During labor, the amniotic fluid can enter the maternal circulation through small tears in the lower uterine segment, at the placental bed, or at a site of uterine trauma [234, 235]. There are two concepts. Mechanical one is that fetal mucin, lanugo hairs, and epithelial squames occluded the pulmonary microcirculation. The other concept is that biologically active substances in the amniotic fluid initiate inflammatory, vasospastic, or procoagulative responses include arachidonic acid metabolites, endothelin, and tissue factor [234].

Clinical Presentation

It typically presents with sudden onset of hypoxia, hypotension with shock, altered mental status, and disseminated intravascular coagulation. Other common signs and symptoms are seizures, evidence of fetal distress, and maternal constitutional symptoms (fever, nausea, and headache).

During pregnancy, at the arrival of the paramedics at the scene of a car crash, the condition is far worse than expected from the injuries sustained, with cardiorespiratory collapse.

> Amniotic fluid embolism should be suspected in every instance of the traumatized pregnant patient who develops signs of respiratory distress with or without right heart strain and disseminated intravascular coagulation.

Diagnosis

There is no specific routine diagnostic test in the clinic to confirm the presence of amniotic fluid embolism. The diagnosis is largely a clinical one and essentially a diagnosis of exclusion. In pregnant trauma patients, other causes of collapse should be ruled out (air or thrombotic emboli, septic shock, hemorrhagic shock, anaphylaxis, uterine rupture, placental abruption, transfusion reaction, and toxicity of anesthetics). Laboratory tests may reveal hypoxemia and typical findings of DIC.

If the mother did not survive, the diagnosis is considered strongly supportive at autopsy when congested lungs are found, and in the pulmonary vasculature, there is mucus and epithelial squames or lanugo hair (Fig. 10.21).

Treatment

Treatment is mainly supportive, aimed at rapid cardiopulmonary stabilization with oxygen, i.v. fluids, and vasopressors. If cardiac arrest occurs, cardiopulmonary resuscitation is initiated. Coagulation factors and blood transfusions may be needed to treat DIC and hemorrhage. Some patients develop renal failure and may need temporary hemodialysis.

If delivery has not yet occurred, emergency CS is essential to prevent further hypoxic damage to the fetus and to facilitate treatment of the mother.

Prognosis

The prognosis of all-cause amniotic fluid embolism is poor. Maternal mortality of traumatic

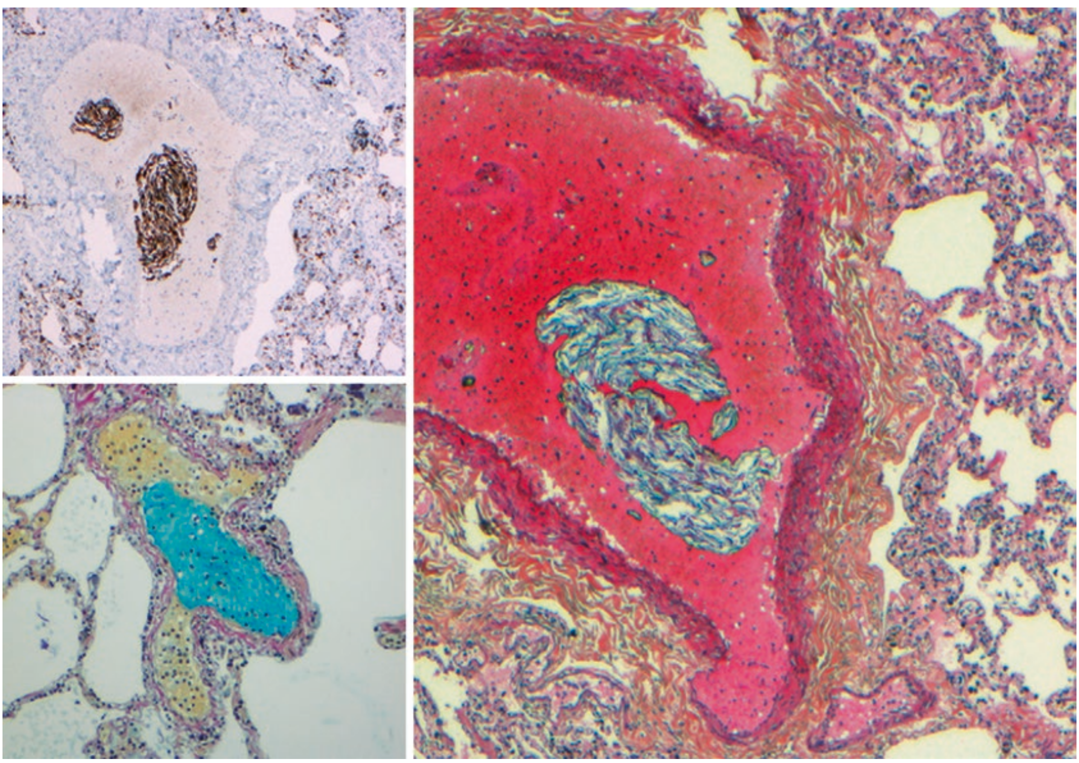

Fig. 10.21 Histological section from the lung showing epithelial squames inside an artery (HES stain, magnification ×4). (*Insert*) Immunohistochemical stain for Pan-cytokeratin, highlighting epithelial squames and Alcian Blue–PAS stain, highlighting mucus. Reproduced with permission from [233]

amniotic fluid embolism is 100%, usually during first several hours [229–231, 233]. Fetal mortality is also 100% [229–231, 233] despite the performance of emergent CS.

10.3.6 Diagnosis

10.3.6.1 Laboratory Findings

- ***Base deficit (BD) > −6*** has probability ≥95% for the absence of intra-abdominal bleeding.
- ***BD ≤ −6*** and ***increased pulse rate*** indicate that there is a markedly enhanced risk for intra-abdominal bleeding.

Decreased BD and/or increased pulse rate was highly sensitive for detecting patients with internal bleeding [236, 237], although both of these studies focused on BD and one [236] has chosen a BD of ≤ −4. BD ≤ −6 had a sensitivity of approximately 88.2% compared with ultrasonography, 76.5% [237]. The latter is due to the fact that ultrasonography is not likely to detect most retroperitoneal or pelvic injuries [238]. However, ultrasonography has a positive predictive value of approximately 100% and nearly equal negative predictive value with BD for detecting free fluid (see Sect. 10.3.6.3). Finally, BD correlates well with blood transfusion and laparotomy requirements (68.4% of patients with BD ≤ −6 indicated for blood transfusion compared with only 1.2% of patients with BD > −6 and 57.9% of patients with BD ≤ −6 indicated for laparotomy compared with only 1.2% of patients with BD > −6). All of these patients whose BDs were ≤ − 6 had intra-abdominal bleeding and undergone a blood transfusion. This fact shows the importance of BD in pregnant patients [237]. A normal BD does not exclude intra-abdominal injury in blunt trauma patients, but the presence of a BD ≤ −6 should be considered a strong indication for abdominal evaluation. A BD of ≤ − 6 has high sensitivity and specificity for detecting free intraperitoneal fluid in patients with blunt abdominal trauma, as well as a high transfusion requirement and laparotomy in these patients.

Hemoglobin and hematocrit levels should be obtained in every patient with blunt abdominal trauma. In 5.4–8% of patients attended by trauma, an undiagnosed pregnancy is found [239]. Serum βHCG levels should be obtained for all females in the reproductive age who were exposed to trauma [240] or selectively if the possibility of conception exists or if amenorrhea is lasting >4 weeks or if the patient is unconscious, and protected X-rays should be obtained as possible.

Up to 16–43.5% of pregnant women with trauma gave a positive response to a drug test (psychotropics, opiates, etc.) [9, 45]. Therefore, in every pregnant trauma patient, especially with head injury with changes in the level of consciousness, serum and/or urine samples of most common drugs should be obtained.

10.3.6.2 Plain Abdominal X-Ray

Plain abdominal X-ray is used for verification of maternal (and fetal) skeletal trauma or maternal pneumoperitoneum from rupture of the hollow viscus. Most common fractures include pelvic ring fractures and diastasis of pubic symphysis (Fig. 10.22).

Fig. 10.22 In the 39th week of her first pregnancy, the patient fell from a standing position and landed on her buttocks with both hips in flexion, abduction and external rotation. AP pelvis X-ray showing the diastasis of the pubis. The sacroiliac joints could not be assessed. The skull of the fetus was high in the pelvis. Reproduced with permission from [241]

10.3.6.3 Transabdominal Ultrasound

Focused abdominal sonography for trauma (FAST) is an important method of evaluating patients with blunt abdominal trauma. Previously reported sensitivities for the detection of free fluid with this method ranged 42–100% [242, 243]. Reported sensitivity in pregnancy is 83% [244]. One explanation for the marked number of false-negative results is that FAST is performed relatively early in the resuscitation process, at a time when hemoperitoneum may not have accumulated to a detectable amount. A marked number of false-negative results (27.5%) are observed in patients with bowel and mesenteric injuries [242].

It is proposed that all hemodynamically stable patients who have sustained blunt abdominal trauma should undergo CT scanning rather than FAST to prevent the possible underdiagnosis of intra-abdominal injury [243]. Only 7–8% of pregnant patients with trauma underwent CT scanning [60, 242]. It appears that the decision to perform a CT examination is arbitrary and may depend on the presence of equivocal objective findings that might result in an unnecessary laparotomy.

Although not as sensitive as CT, FAST has a distinct advantage over CT in the rapid triage of unstable patients with blunt trauma who cannot safely travel to the CT suite. Detection of free fluid and/or parenchymal abnormality results in safer and faster disposition to the operating room than could be accomplished with either CT or diagnostic peritoneal lavage. If no free fluid is detected, the patient may be transferred to the labor and delivery area for fetal monitoring and potential delivery. In the future, sonography performed with contrast material may be a viable alternative to CT.

Pelvic Free Fluid

US examination of the pregnant abdomen to detect FF is much more useful than clinical examination. Varying amounts of FF have been detected during the menstrual cycle, with the greatest volume detected during ovulation [245, 246]. This FF is presumed to serve the teleological purpose of transporting the ovum by wave motion [245]. Prevalence of transient physiological FF on transabdominal ultrasonography in reproductive women has been estimated to range 36–40%. The estimated mean volume ranges 5–21 mL [245–249]. This phenomenon has been attributed to:

- Fluid secondary to follicular rupture [246]
- Ovarian fluid exudation secondary to increased capillary permeability under the influence of estrogen [246, 247]
- The blood secondary to retrograde menstruation [250]

The amount of peritoneal FF seemed to decrease significantly after the peak, near menstruation [246, 247]. In a study by Ormsby et al. [251], detection of FF in (a) both the abdomen and pelvis had the highest association with intra-abdominal injury, followed by (b) FF isolated to abdomen and then (c) isolated to pelvis, and the least is (d) when there was no FF. The FF most often occurs at the site of organ injury and also within the pelvis [252]. There is no difference in injury rate between those with isolated pelvic FF and those without FF and that isolated pelvic FF is not likely to be associated with intra-abdominal injury [253]. These findings differ from Ormsby et al. in that isolated pelvic FF had a statistically significant higher injury rate than those without FF in pregnant and nonpregnant women. The discrepancy between previous findings [253] and findings by Ormsby et al. regarding isolated pelvic FF among nonpregnant patients may be due to several factors. Sirlin et al. had only 8% of pregnant patients. In a study by Ormsby et al. [251], there was a larger sample size with 16% of pregnant women. Physiological FF is detected mostly during ovulation and a few days after ovulation in 36–40% of nonpregnant women [245]. Therefore, outside of their ovulation period, these women would not be likely to have sonographically detectable amounts of physiological FF. Unfortunately, authors did not query the menstrual history of their study subjects. Therefore, it is impossible to know if there were a greater percentage of women who were anovulatory and/or were in a time period of their menstrual cycle when physiological FF is less likely to be seen.

Transabdominal sonography is less sensitive than transvaginal sonography in detecting pelvic FF [248, 249]. The sensitivity of the pelvic view on transabdominal ultrasound imaging for the detection of FF was 73–129 mL [254]. This is much larger than the average 7–21 mL of physiological fluid aspirated from the cul-de-sac of women [246–249]. Thus, any trace FF in the pelvis on the FAST exam in the setting of blunt abdominal trauma may indicate the FF level is not physiological. Although more likely to detect small volumes of pelvic FF, transvaginal ultrasonography is impractical, as it would be difficult to perform in the active trauma resuscitation setting. Furthermore, trauma patients undergoing FAST do not always have the benefit of having a completely full bladder. Therefore, FAST would not be expected to reliably detect small amounts of FF that would be detected during a detailed comprehensive transvaginal ultrasound examination. In pregnant patients, small amounts of pelvic FF may be missed due to a mass effect of the enlarging uterus [255]. The ultrasound was less sensitive for detection of intra-abdominal injury in pregnant versus nonpregnant female patients [242]. Another possible explanation of missed pelvic FF is adequate bladder distention during the ultrasound. The use of a full bladder technique increases detection of pelvic FF, and a minimal amount is often physiological [253]. A significant cause for missing pelvic FF was the bladder not being distended enough to provide an adequate acoustic window [256]. Patients with blunt abdominal trauma often have a Foley catheter, which decompresses the bladder. Without a full bladder as an acoustic window, FF in the pelvis may be overlooked with transabdominal ultrasound. This may explain why some patients had false-negative FAST in the group without FF in the study by Ormsby et al. Of the nine false-negative cases in pregnant patients, 67% were due to placental abruption, and it has been proven that ultrasound is not sensitive for detection of placental abruption [257]. For these patients, careful clinical correlation such as gestational age, significant vaginal bleeding, fetal distress, and/or severe abdominal pain should be made. If placental abruption were excluded for the group comparison, pregnant patients in a group without FF would have an injury rate of 1% with no change for the group where the fluid was isolated to the pelvis. Without a full bladder, only larger amounts of FF could be detected. Isolated pelvic FF is the second most common true-positive fluid accumulation pattern [242].

The ability to distinguish between physiological FF and FF resulting from injury has been previously addressed. Sirlin et al. reported isolated FF in the cul-de-sac in 56 patients, and only two had injuries, but they made no distinction between pregnant and nonpregnant patients [253]. Their conclusion was that isolated FF in the pelvis was likely to be physiological and not due to injury. In another study, 54% of the false-positive US examinations in pregnant and nonpregnant patients combined revealed isolated FF in the pelvis [242]. Also of interest in the same study are the three patients with undiagnosed ectopic pregnancies that ruptured after their traumatic events. The incidence of ectopic pregnancy has steadily increased over the past three decades, and these patients are seen more frequently in the acute care setting [258]. The transvaginal US has been the imaging study of choice for detecting an ectopic pregnancy, but less is known regarding transabdominal US [259]. Isolated FF in the pelvis cannot necessarily be discounted as being physiological in the pregnant patient [242]. If FF is present in the left upper quadrant, in both upper quadrants, or diffusely, it is significantly associated with splenic injuries [242, 252].

The dynamics of flow in the abdomen are of interest in that FF tended to flow from the left to the right upper quadrant rather than down the left paracolic gutter into the pelvis. One explanation for this may be that hemorrhage from the spleen first accumulates in the left and then progresses to the right upper quadrant because the phrenicocolic ligament acts as a relative barrier to the movement of fluid to the left gutter [260]. It also appears that fluid from the right upper quadrant flowed down the right paracolic gutter rather than toward the left upper quadrant, perhaps because of the gravity dependence of the right paracolic gutter and pelvis. The most common pattern of FF accumulation in pregnant patients with fetuses

of all gestational ages is a pattern of accumulation in the left and right upper quadrants and the pelvis (Figs. 10.23 and 10.24).

However, US depicted pelvic FF in pregnant patients in the third trimester, and the sensitivity of focused abdominal US for trauma was the highest for patients who were in the first trimester of pregnancy. One possible explanation for this may be that the compression of intra-abdominal structures, specifically the paracolic gutters, by the expanding uterus may make it more difficult to detect FF in the paracolic gutters and pelvis [261]. It has been suggested in the past that the fetus is well protected against injury from blunt trauma because it is encased in a fluid-filled structure [8]. It was shown that intra-abdominal injuries in pregnant patients were most common to the spleen or placenta, necessitating precipitous delivery or resulting in fetal demise [242]. Thus, the shear forces present in even low-force injuries such as falls cannot be discounted, and it is recommended that US, as well as fetal monitoring for patients whose fetuses are past 20 weeks of gestation, should routinely be used in pregnant patients with trauma. Continuous

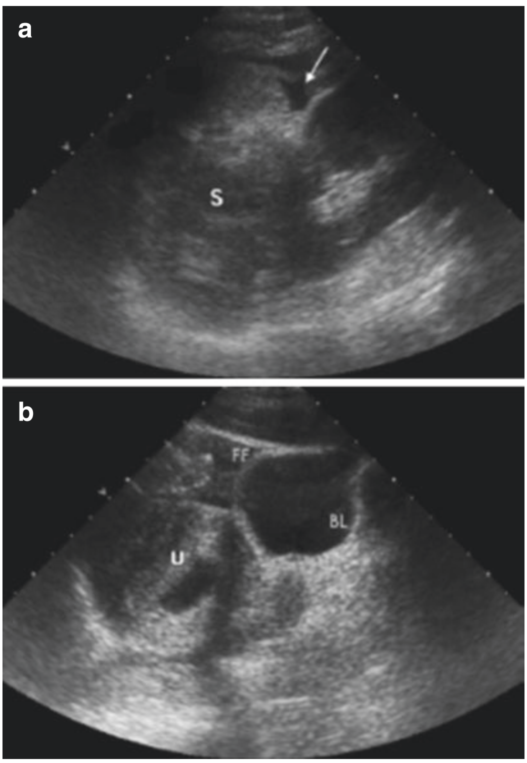

Fig. 10.23 The first-trimester blunt abdominal trauma with a splenic laceration in a motor vehicle collision. (**a**) Longitudinal US image of left upper quadrant reveals perisplenic free fluid (*arrow*) and abnormal-appearing splenic parenchyma (*S*). (**b**) Longitudinal US image of pelvis shows free fluid (*FF*) superior to the bladder (*BL*) and gravid uterus (*U*). Reproduced with permission from [242]

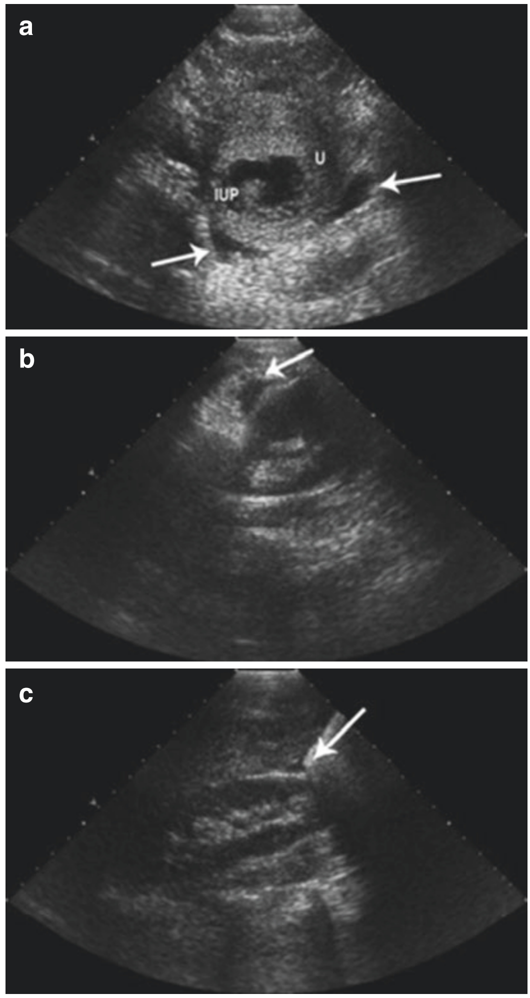

Fig. 10.24 A first-trimester high-speed motor vehicle accident with spleen laceration. (**a**) Transverse scan of the pelvis with empty bladder shows early intrauterine pregnancy and bilateral free fluid (*FF*) (*arrows*) adjacent to the uterus. (**b**) Transverse scan of the left upper quadrant demonstrates FF (*arrow*). (**c**) A longitudinal scan of the right upper quadrant demonstrates FF (*arrow*) in the hepatorenal fossa. *IUP* intrauterine pregnancy, *U* uterus. Reproduced with permission from [251]

fetal monitoring is more sensitive but is less specific than the US for the detection of placental abruption [59].

> FAST examination to detect FF in pregnant trauma patients found a reasonable specificity and accuracy (>90%) but, not surprisingly, a rather low sensitivity (61%), demonstrating that the FAST examination remains a reasonable screening tool for intraperitoneal hemorrhage but that it does not rule out intra-abdominal pathology [242].

Spleen

The spleen (Fig. 10.25) and liver are most likely to be damaged in later stages of pregnancy, as they are displaced by the expanded uterus closer to the chest wall. Although there are no guidelines on the management of specific injuries in the pregnant patient, there is experience with successful nonoperative management of stable patients in pregnancy [262]. With the concomitant head injury, intervention with either embolization or splenectomy is recommended (see Chap. 9). This approach is designed to prevent hypotension and instability, which would worsen the prognosis of their head injury. Likewise, one could argue that the risk to the viable fetus from ongoing hemodynamic instability may warrant adopting a more aggressive approach in the management of traumatic injuries in the mother.

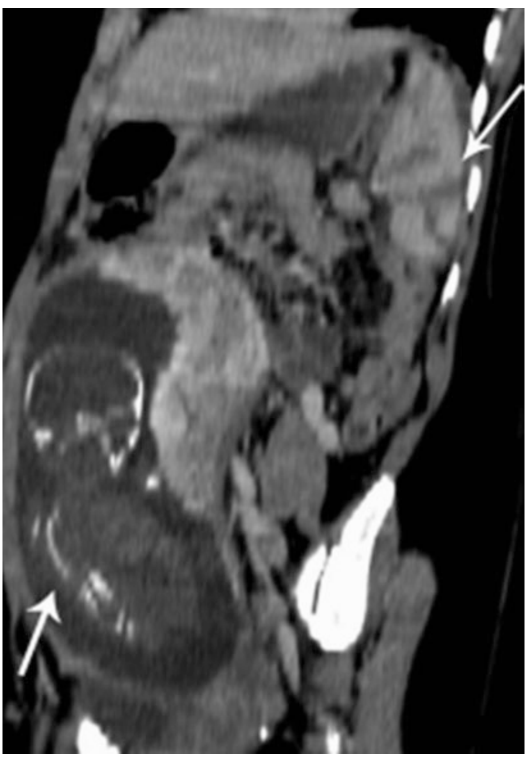

Fig. 10.25 An oblique sagittal CT scan image showing traumatic splenic laceration (*right arrow*) and the 26-week fetus (*left arrow*). Reproduced with permission from [263]

Placental Abruption

The sensitivity of US to identify post-traumatic abruption is only 40–50% [15, 59]. Therefore, the absence of visualization of subchorionic hemorrhage or a retroplacental clot (Figs. 10.26 and 10.27) on the US in the presence of clinical symptoms like abdominal pain mandates further continuous fetal monitoring with a low threshold to intervene should signs of fetal distress appear or abdominal CT scan should be performed. It is

Fig. 10.26 Placental abruption. Emergency ultrasound performed in the trauma bay reveals presence of anechoic pockets representing hematoma separating the placenta (*P*) from the myometrium (*M*). Reproduced with permission from [263]

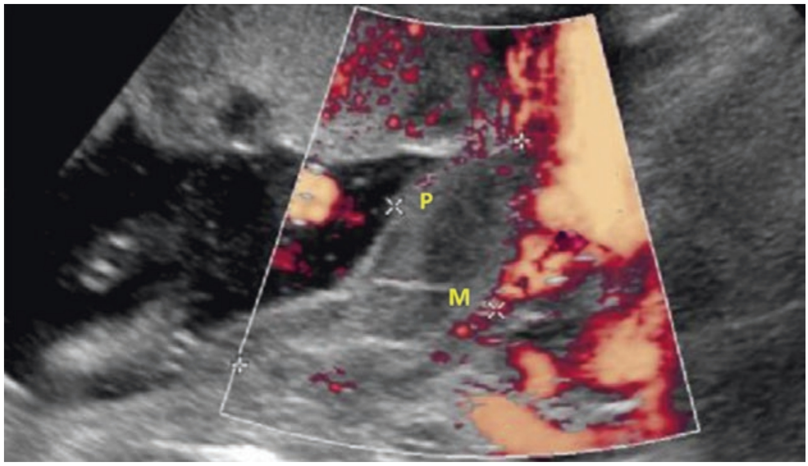

Fig. 10.27 Placental abruption. A 21-week pregnant patient. A heterogeneous collection is seen interposed between the placental edge (*P*) and the myometrium (*M*). The collection lifts the placental edge away from the underlying myometrium. Reproduced with permission from [263]

important to stress that acute placental abruptions can be seen on the US as an echogenic retroplacental mass, which then becomes hypoechoic in 1–2 weeks mimicking fibroids.

10.3.6.4 Cardiotocography

Ultimately, complete placental separation and fetal demise will occur as the process of placental abruption continues. Depending on the size of the initial clot, placental abruption might not be infrequently asymptomatic in its early stages. Owing to the high thromboplastin concentration in the surrounding trophoblastic tissue, local DIC is likely to develop leading to expansion of the clot. With the expansion of the retroplacental clot, uterine activity will usually emerge. With >8 contractions/h and in the absence of reassuring fetal monitoring, there is a 25% chance of finding placental abruption in pregnant women after blunt abdominal trauma [59]. Changes in fetal CTG, such as bradycardia (<110 bpm), loss of beat-to-beat variation, or sinusoidal patterns, may indicate placental injury, fetal hypoxia, or fetal blood loss.

10.3.6.5 Doppler Ultrasound

Doppler US has been found to be potentially useful in the screening of pregnancies at risk for complications dealing with abnormal placentation [264]. In the future, this technique may possibly be applied in emergency situations to the detection of traumatic abruption, though it is unknown how its performance would compare with CT scanning and how it may improve diagnosis as an adjunct diagnostic imaging modality.

10.3.6.6 Abdominal CT

Placental Abruption

The utility of this modality during pregnancy has been limited due to concerns for teratogenicity and childhood cancers caused by fetal irradiation, which is thought to be most detrimental in early pregnancy. As a result, there have been few CT studies of normal and abnormal placental anatomy [265, 266], which in turn may lead to unsatisfactory evaluation of placental abnormalities. Because the normal gravid uterus and physiological changes during pregnancy often confound the interpretation of CT studies, it is also useful to define the anatomical variations associated with normal placental development [267].

True placental abruptions were characterized by large, contiguous, and retroplacental and/or full-thickness areas of low enhancement that form acute angles with myometrium (Fig. 10.28). Some large abruptions remained undetected likely due to the lack of systematic evaluation of the placenta. False-positive results required additional obstetrical monitoring overnight. This is an acceptable cost compared to the catastrophic consequences of missing an abruption. Aberrations in fetal heart rate have been shown to correlate with the severity of placental abruption

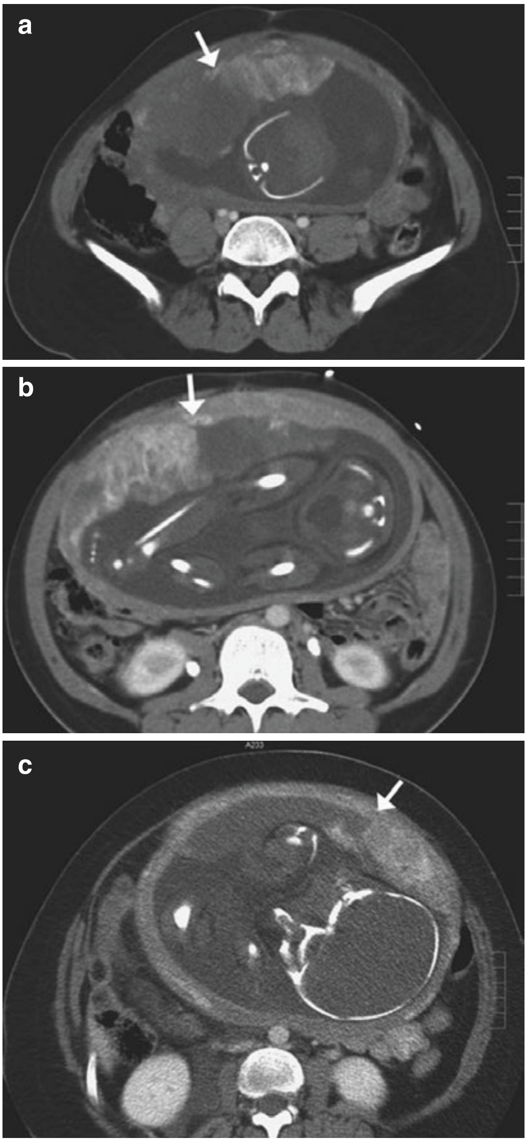

Fig. 10.28 CT scans of traumatic placental abruptions. (**a**) At 23 weeks of gestation, right-sided placental hematoma is present. (**b**) At 29 weeks of gestation, absence of perfusion in the anterior placenta is evident. (**c**) At 36 weeks of gestation, heterogeneous placental enhancement and relative area of decreased enhancement anteriorly correlate with abruption. *White arrows* mark the border between non-perfused and perfused regions of the placenta. Reproduced with permission from [269]

[268] and may serve as a useful tool to differentiate between false-positive results and true abruptions diagnosed by CT scan. The sensitivity of the CT for placental abruption is near 100% with somewhat lower specificity [269].

10.3.7 Treatment

10.3.7.1 Observation

There is much controversy regarding the optimum duration of observation needed in the gravid woman who has had any form of trauma. The controversy results from the fact that the frequency and onset of adverse outcomes are uncertain. This uncertainty has led to the development of many different protocols for the management of the pregnant patient with trauma. Over three-quarters of women were admitted for only 1 day following MVA. Although the optimal length of time necessary to monitor women in hospital with minor or no obvious injuries following an MVA cannot be determined in one study, it would suggest that 1 day is sufficient in most cases, without any adverse impact on complication rates [5]. The management of pregnant trauma patients may be assisted if we stratify injured women into four groups [49]. The first is comprised of injured women who are unaware that they are pregnant (incidental pregnancy).

Since routine radiographic studies have the greatest teratogenic potential in early pregnancy, a pregnancy test should be obtained from all trauma patients of reproductive age. The second group is pregnant women of less than 24–25 weeks of gestation where the primary focus is aimed solely at the mother since the fetus has not yet reached the border of viability. The third group consists of pregnant women at a gestational age beyond the border of viability. For this group, monitoring, support, and clinical consideration are aimed at two patients, the mother and fetus. The fourth group is comprised of severely injured women who present in a perimortem state. In these patients, early CS may facilitate maternal resuscitation and increases the chance of fetal survival. Radiologic examination in this group is contraindicated because perimortem CS should be performed within 4–5 min of maternal (unsuccessful) CPR.

10.3.7.2 Radiologic Interventional Techniques

Classified as zone 3 of the retroperitoneum, hemorrhage into the pelvis is difficult to control operatively and is usually managed with interventional

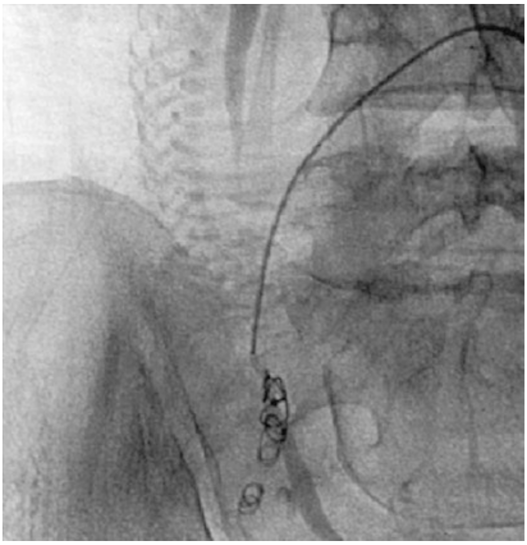

Fig. 10.29 Fluoroscopic image of embolization of the right iliac artery shows fetal spine over the right iliac crest. Reproduced with permission from [270]

embolization (Fig. 10.29) if there is no indication for the operative fixation of the pelvic fracture (see Sect. Pelvic Fracture Treatment) which, apart from bone stabilization, also stabilizes retroperitoneal hematoma. The radiation dose required for the interventional radiologic procedure(s), however, can be prohibitive.

10.3.7.3 Surgical Treatment

Initial Stabilization

Management of maternal cardiac arrest is presented in Fig. 10.3. Rapid maternal respiratory support is critical; anoxia occurs more quickly (especially in advanced pregnancy): as (1) oxygen consumption increases by almost 20% during pregnancy to meet the increased metabolic demands of the placenta, fetus, and maternal organs [271] and (2) as functional residual capacity may be significantly reduced due to elevation of the diaphragm. This leads to increased minute ventilation leading to a compensatory respiratory alkalosis, which in turn decreases the maternal capacity to buffer acidosis from shock. This leads to more rapid respiratory decompensation, particularly with chest trauma, so supplemental oxygen should be given to maintain maternal oxygen saturation >95% to ensure adequate fetal oxygenation (Fig. 10.30) [272, 273].

Evaluation of the fetus should begin only after the mother has been stabilized. Supplemental oxygen and intravenous fluids are administered initially and are continued until hypovolemia, hypoxia, and fetal distress resolve [121]. Two large bore (14–16 gauge) i.v. lines should be placed in a seriously injured pregnant woman [272]. These measures maximize uterine perfusion and oxygenation for the fetus [121]. In animal studies, improvement in fetal partial pressure of arterial oxygen or fetal heart rate is slower with the use of saline or lactated Ringer's solution than with blood replacement attesting to the importance of restoring oxygen-carrying capacity as well as blood volume [51, 53].

Because of the increased blood volume late in pregnancy, the mother may not show typical signs of hypovolemia, even with the loss of a large volume of blood (up to 2000 mL). However, uterine perfusion still may be compromised.

> Uterine blood flow may decrease by up to 30% before the mother demonstrates clinical signs of shock. Therefore, blood transfusion should be initiated when significant blood loss has occurred or is suspected. Crystalloid is effective in improving neonatal oxygenation if there is evidence of maternal hypotension, but if hypotension is suspected to be due to hemorrhage, O-negative blood is the resuscitation fluid of choice.

It is important to recognize that significant blood loss can occur in the uterine wall or retroperitoneal space without external bleeding. After 20 weeks of gestation, the uterus may compress the great vessels when a pregnant woman is supine. This compression can cause a decrease of up to 30 mmHg in maternal systolic blood pressure, a 30% decrease in stroke volume [273], and a consequent decrease in uterine blood flow [121]. Manual deflection of the uterus laterally or placement of the patient in the lateral decubitus position avoids uterine compression [121].

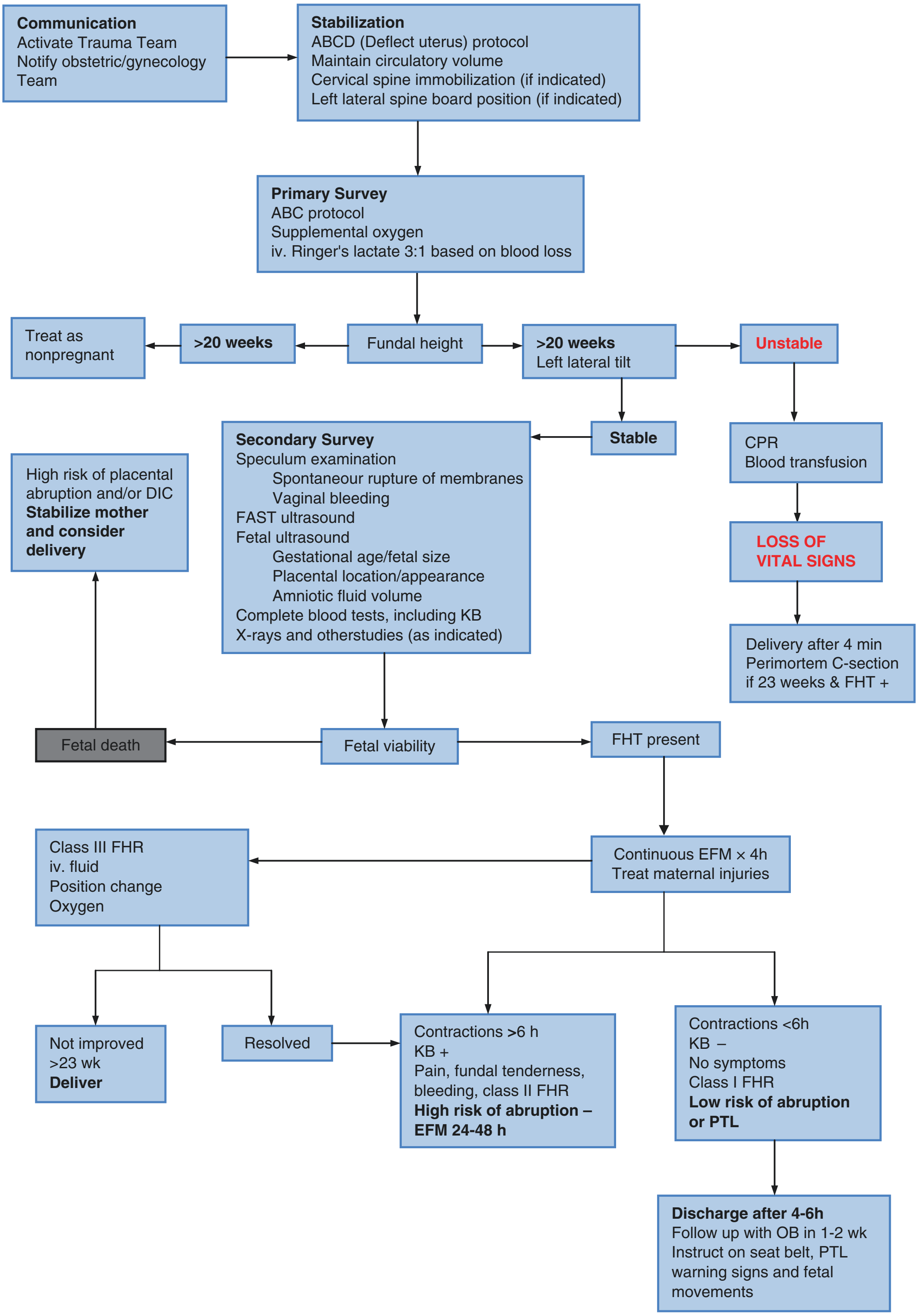

Fig. 10.30 Algorithm for the management of the pregnant woman after *blunt* (abdominal) trauma. Modified with permission from [274–276]; *KB* Kleihauer–Betke test, *FHT* fetal heart tones, *EFM* electronic fetal monitoring, *PTL* preterm labor. If Kleihauer–Betke test is positive, the treatment plan should follow instructions presented in Fig. 10.20

Because of their adverse effect on uteroplacental perfusion, vasopressors in pregnant women should be used only for intractable hypotension that is unresponsive to fluid resuscitation [272].

Secondary Assessment

After initial stabilization, other maternal injuries are evaluated, and fetal heart tones (FHTs) are assessed by Doppler or ultrasonography. If FHTs are absent, resuscitation of the fetus should not be attempted. There were no fetal survivors in a series of 441 pregnant trauma patients with initially absent FHTs [277]. When FHTs are present, gestational age is determined by fundal height, history, Leopold's maneuvers, or ultrasonography [277]. Ultrasonography is the most accurate method of determining gestational age. Determination of fetal viability is subject to institutional variation: an estimated gestational age of 24–26 weeks and an estimated fetal weight of 500 g are commonly used thresholds of viability. Only viable fetuses are monitored [277], because no obstetric intervention will alter the outcome with a previable fetus. The findings of the physical examination in the pregnant woman with blunt trauma are not reliable in predicting adverse obstetric outcomes [13, 59]. Pregnancy induces physiological changes in women (Table 10.4). For example, maternal blood pressure does not accurately reflect uterine perfusion or fetal injury [34, 35, 239], because pregnant women can lose up to 30% (2000 mL) of their blood volume before vital signs change. Blood transfusions should be administered according to standard guidelines, but the mother's Rh status must be considered. If it is unknown, Rh− blood should be administered. Invasive hemodynamic monitoring should be considered early during resuscitation to ensure adequate volume resuscitation [121]. Compared with nonpregnant persons who experience trauma, pregnant women have a higher incidence of serious abdominal injury but a lower incidence of chest and head injuries [4]. Maternal pelvic fractures, particularly in late pregnancy, are associated with bladder injury, urethral injury, retroperitoneal bleeding, and fetal skull fracture [121]. After 12 weeks of gestation, the maternal uterus and bladder are no longer exclusively pelvic organs and are more susceptible to direct injury [37]. Skull fracture is the most common direct fetal injury, with a mortality rate of 42% [34]. Altered mental status or severe head injury after trauma in a pregnant woman is associated with increased adverse fetal outcomes [51]. Placental abruptions usually occur from 16 weeks of gestation onward [37]. Some signs of placental abruption, including spontaneous rupture of membranes, vaginal bleeding, and uterine tenderness, are infrequent after trauma [4, 15, 32, 59]. Although associated with maternal and fetal morbidity [46, 183], these signs are only 52% sensitive and 48% specific for adverse fetal outcomes [13].

Pelvic Fracture Treatment

Current guidelines are recommended in the hemodynamically unstable, nonpregnant patient who sustained severe pelvic trauma and has no other identifiable source of bleeding (patients with negative diagnostic peritoneal lavage and/or FAST examination) control of pelvic or retroperitoneal hemorrhage via embolization of pelvic vessels during angiography, in particular of the hypogastric arteries [278]. Although successful pregnancies after prior occlusion of both hypogastric arteries have been described, there are no reports on the safety and efficacy of angioembolization for acute pelvic hemorrhage in pregnant patients.

Pelvic and acetabular fracture surgery in pregnancy is performed infrequently [149, 153, 279, 280]. There are considerations against performing surgery during pregnancy. Such surgery is usually associated with an increased complication rate [149]. Another consideration against surgical treatment is concern over causing direct intraoperative injury to the uterus. In some cases, the mother's general condition, affected by other injuries, coagulopathy, or hemodynamic instability, does not permit surgical intervention [153]. Acetabular fracture treatment was reported in 83.3%, with skeletal traction and open reduction and internal fixation performed equally frequent [149]. Unstable fractures of the pelvic ring can be safely treated with open and percutaneous osteosynthetic techniques resulting in favorable pregnancy outcome [153, 279, 280]. Vertically unstable fracture of the posterior pelvic ring using a low-exposure technique and

imaging restricted to the posterior ring can be performed [280]. External fixation of unstable pelvic fractures in pregnant patients is a viable option with good outcomes [262].

Management of disruption of symphysis pubis is generally nonsurgical (bed rest, pelvic binders, ambulation devices). External fixation is recommended when lesions are unstable, when the inadequate reduction is achieved or when the diastasis is more than 4 cm [281]. Vertical displacement of the pubic rami associated to a widening of the sacroiliac joint means a disruption of the pelvic ring and may be treated with a pelvic fixator [282]. In addition, in cases of severe pain after conservative treatment, it may be necessary to perform an open reduction and internal fixation [283]. If operative treatment is indicated without fetal distress or placental abruption, vaginal delivery is recommended followed by operative reduction of the diastasis. If CS is indicated, standard Pfannenstiel incision is made for both procedures because it allows easy access to the uterus and symphysis.

Damage Control Surgery

> *The only weapon with which the unconscious patient can immediately retaliate upon the incompetent surgeon is a hemorrhage.*
>
> William Stewart Halsted, 1912

Damage control surgery is defined as the rapid termination of an operation after the control of life-threatening bleeding and intestinal spillage, followed by correction of physiological abnormalities which precedes definitive management of initial injuries [284]. It is best defined as creating a stable anatomic environment to prevent the patient from progressing to an unsalvageable metabolic state when patients are more likely to die from metabolic failure than from failure to complete organ repair [285]. This modern strategy involves a staged approach to multiply injured patients. Damage control surgery is designed to avoid or correct the lethal triad of hypothermia, acidosis, and coagulopathy during or before definite injury management. The concept of abbreviated laparotomy was first described by Stone in 1983 [286]. Any laparotomy was terminated with temporizing measures when coagulopathy was noted.

These involved packing of the abdominal cavity in the majority of the cases to stop bleeding and scheduled return to the operating room. The term "damage control" was popularized by Rotondo and Schwab, who in 1993 outlined a three-phase approach to patients with major abdominal injuries [287]. Phase one consisted of control of hemorrhage and contamination with rapid techniques of intra-abdominal packing and stapling intestinal ends, followed by temporary abdominal closure. Phase two in the ICU addressed restoration of a physiological environment, in particular, temperature, coagulation, and optimization of oxygen delivery. Phase three occurred, usually within 24–36 h, with the removal of abdominal packs, restoration of intestinal continuity, and definitive surgery with abdominal closure. The concept of damage control was expanded further in 2001 by Johnson who added a fourth phase at the beginning called "ground zero" [288]. The principles of "ground zero" damage control include rapid transport to the hospital and early decision-making to facilitate hemorrhage control, prevention of hypothermia, and utilization of massive transfusion protocols. Since the early 1990s, several series have consistently demonstrated superior survival rates of patients with blunt and penetrating trauma in whom principles of damage control surgery had been employed. Accepted clinical and laboratory parameters for the application of principles of damage control surgery are the following:

- Hypotension: SBP <90 mmHg
- Hypothermia: T <34 °C
- Coagulopathy: activated partial prothrombin time (aPPT) >60 s
- Acidosis: pH <7.2 or arterial base deficit (BE) ≥8
- Major intra-abdominal vascular injury
- The associated need for management of extra-abdominal life-threatening injury (e.g., concomitant thoracic injuries)

Choosing the right patient for damage control is challenging. Awareness of potential triggers to initiate damage control is vital. Preemptive decision-making to implement damage control should occur early rather than at a delayed point when the patient is in extremis.

Reports on damage control surgery in pregnancy are rare and mostly limited to liver injuries and spontaneous liver rupture complicated by HELLP syndrome (see Chap. 11). Anecdotal case reports or case series describe successful management of liver or splenic injuries with a planned staged approach (abbreviated laparotomy and scheduled return to the operating room) [289]. Pregnancy should not influence the decision to employ principles of damage control in a severely injured woman. In fact, hypotension, coagulopathy, and acidosis, all which show or develop in a pregnant woman at a later state, ask for a more proactive approach.

Although not addressed in the recent literature, one of the main controversies of damage control surgery in the pregnant woman concerns the timing of delivery. Since most authorities agree on the fact that delivery of the fetus in maternal extremes should be part of resuscitation because of recruitment of the uteroplacental blood volume to the maternal circulation, delivery of a term or near-term fetus should be regarded as part of the damage control approach. The situation in the severely preterm infant is more complex. Assuming that damage control surgery is exclusively employed in the catastrophic abdominal or thoracic injuries with ongoing bleeding, one would accept that the hemodynamic instability of the mother in these situations mandates the use of all possible resuscitative efforts including CS of a premature fetus. However, that delivery of a preterm fetus is not always mandatory in the setting of damage control surgery [290]. A fetal gestation could be safely prolonged after 28 weeks of gestation.

10.3.7.4 Obstetric Management

Fetal Monitoring

Obstetric sonogram should be performed to assess fetal viability, fetal age, and fetal well-being [14]. Evaluation of fetal trunk and extremity movement, fetal breathing activity, amniotic fluid volume, and fetal heart rate changes with fetal movement will establish fetal well-being. Around 24% of pregnant trauma patients admitted to the hospital will deliver at the trauma hospitalization [6, 107]. Therefore any viable fetus of 24 weeks or more requires cardiotocographic (CTG) monitoring after maternal trauma even with no obvious signs of abdominal injury [15, 33].

> Continuous electronic fetal monitoring is more sensitive in detecting placental abruption than ultrasonography, intermittent monitoring, an acid elution test (Kleihauer–Betke test to assess the amount of fetal blood in the maternal serum), or physical examination [33].

Monitoring is initiated as soon as possible after maternal stabilization [33, 121, 277] because most placental abruptions occur shortly after trauma [4]. The ideal duration for electronic fetal monitoring is unclear [13, 25, 33, 34]. The recommendation is a minimum of 4 h of CTG monitoring [59], while others recommend 6 h [33, 107]. This should be extended to 24 h if at any time during the first 6 h there is more than one uterine contraction every 15 min (≥5/h), uterine tenderness, nonreassuring fetal CTG monitoring, vaginal bleeding, rupture of the membranes, or any serious maternal injury (Fig. 10.30). This widely used protocol (Fig. 10.30) has a sensitivity of 100% (>20 weeks of gestation) for predicting adverse outcomes within 4 h [59].

Occasional uterine contractions are the most common finding after trauma in pregnancy [4, 13, 32, 59]. These occasional contractions are not associated with adverse fetal outcomes [4, 33] and resolve within a few hours in 90% of cases [59]. The occurrence of ≥8 uterine contractions per hour for more than 4 h, however, is associated with placental abruption [59]. With placental abruptions after trauma, there is a 67–75% rate of fetal mortality [4, 46]. If significant placental abruption occurs, a viable fetus

should be delivered immediately, and 69% of fetal deaths can be prevented by CS [291]. Bradycardia or repetitive late decelerations unresponsive to intrauterine resuscitation also require immediate delivery of the fetus if the mother is stable [277].

Around 70% of patients required more than 4 h of fetal monitoring because of continued contractions (≥4/h), abnormal laboratory values, or vaginal bleeding. All patients discharged at the end of 4 or 24 h had similar outcomes compared with noninjured control patients [59]. If fetal tachycardia is present or a nonstress test is nonreactive, monitoring usually is continued for 24 h, but no studies exist to support or refute this practice. Some recommend prolonged electronic fetal monitoring in patients with high-risk mechanisms of injury: automobile versus pedestrian and high-speed MVAs [33]. No evidence supports the use of routine electronic fetal monitoring for more than 24 h after noncatastrophic trauma [13]. It can prevent only a few perinatal deaths and is most useful for determining the reassuring fetal status and appropriate discharge [13]. Abnormal tracings (3.1% of pregnant women with traumatic injury) are not reliable in predicting adverse fetal outcomes (sensitivity 62%, specificity 49%) [4, 13]. In contrast, a normal tracing has a negative predictive value of 100% when combined with a normal physical examination [13].

Patients who enter preterm labor and those at risk of developing contractions (i.e., gestational age >35 weeks, victims of assault, and pedestrians hit by motor vehicles) should also be monitored for 24 h [33]. If formal continuous fetal monitoring is not available, periodic Doppler measurement or bedside ultrasound calculation of a fetal heart rate is an appropriate temporary substitute. Fetal sonography may provide the presence of liver [292] or extensive brain injury [146, 293].

> Beware of the potentially tachycardiac maternal heart rate in pregnant trauma victims. Comparison of the fetal heart rate heard with the Doppler with the maternal pulse on the cardiac monitor can help ensure that it is the fetus's pulse being measured.

Pelvic Fractures

The recommended method of delivery for pelvic fractures during pregnancy depends on the presence of initial fetal and maternal distress, the degree of fetal maturity, the maternal ISS, the displacement of the pelvic or acetabular fracture, and the eventual course of labor. Because these fractures tend to heal within 8–12 weeks, vaginal delivery should not be contraindicated after fractures that occurred earlier in pregnancy. Pubic ramus fractures adjacent to the urethra or bladder, severe lateral compression fractures, and acute fractures of the pelvis with marked displacement may be relative indications for CS if labor starts in a viable pregnancy. Eastman in 1958 stated that in 5–10% of cases, CS will be necessary because of pelvic deformity after fracture. Others stated that delivery through a recently fractured pelvis is apparently not attended by serious complications and vaginal delivery should be permitted in the absence of gross pelvic deformity [294, 295]. Bladder and urethral injury after delivery through a recently fractured pelvis have been reported [295]. The separation or displacement of fractures around the symphysis pubis jeopardizes the urethra and bladder when the presenting part descends during labor [296]. Fortunately, vaginal delivery was successful in 75% of pelvic fractures that occurred in the third trimester [149].

Postpartum Care

Placental Abruption

After delivery, a patient's hemodynamic status should be carefully monitored. Judicious use of transfusion or diuretics may be required, based on central hemodynamic monitoring indices, hemoglobin concentration, and urine output. If vaginal delivery is accomplished quickly without trauma, prompt restoration of the hemostatic mechanism usually results. Even in the most severe cases, clinically evident coagulopathy usually resolves by 12 h after delivery. Fresh frozen plasma or platelet transfusions occasionally are necessary to hasten the process. Suboptimal clotting may be present at the time of delivery, and wounds must be carefully inspected for evidence of hematoma formation. Early ambulation should be practiced due to the

phenomenon of rebound hypercoagulability in patients recovering from DIC [297]. Pulmonary status must be carefully monitored, especially if the patient has had rapid induction of general anesthesia and is at risk for aspiration pneumonia. Patients may have acute renal failure as a result of hypovolemia and vasospasm. Fortunately, this condition generally is reversible with proper management.

10.3.8 Prognosis

In the past, most causes of maternal death were obstetric and due to a lack of prenatal care and inadequate assistance during delivery. Because of improved medical services, hospital deliveries, and reduced parity, a significant reduction in maternal mortality was noted. Although a remarkable decline in maternal mortality in the United States during the twentieth century was evident, little progress has been made during the last two decades in the twentieth century [298]. In fact, according to Centers for Disease Control and Prevention, there has been a slight increase in this rate over the past few years, reaching 13 deaths/100,000 births in 2004. Trauma complicates up to 7% of all pregnancies and is the leading cause of nonobstetric maternal deaths, accounting for around 46% of all maternal deaths [8, 299–301]. Pregnancy and childbirth remain serious life-threatening events for many women in low-income countries, maternal deaths contributing to as many as 25% of all deaths of women of reproductive age [302]. The death of a woman in childbirth signifies far more than the tragic loss of a single life; it can threaten the survival of the whole family, especially the newborn baby and other young children. The risk for pregnancy in "minor" or noncatastrophic trauma is still significant, with preterm labor occurring in 8%, placental abruption in 1%, and fetal death in 1%. For those with major trauma, maternal mortality is about 9% [4], and the fetal death rate is 20% or greater.

10.3.8.1 Blunt Trauma in General

Maternal Outcome

Trauma is the most common cause of maternal mortality with the incidence of 46.3% [8]. In other words, 24% of patients sustaining a major blunt trauma in pregnancy died [303]. The major injury was defined as documented shock at the time of admission, skull fracture, cerebral contusion or intracerebral hemorrhage, spinal column fracture and/or injury, chest injury necessitating thoracotomy or tube thoracostomy, injury of the abdominal viscera or genitourinary tract treated operatively, or a pelvic fracture. In 1971, maternal mortality of 7% was reported in serious automobile injuries and a 14% injury rate in surviving mothers [135]. Head injury is the most common cause of maternal death, followed closely by hemorrhagic shock [7, 179, 304]. Maternal hemorrhagic shock carries a maternal mortality rate of 66.6% [305]. Serious injuries (high ISS values) result in higher mortality rate (Fig. 10.31), but this mortality rate in pregnant women is comparable with nonpregnant. When injury type is examined, maternal and fetal death is highest with internal injuries to the thorax, abdomen, and pelvis.

Fetal Outcome

Trauma increases the rate of fetal loss and placental abruption over baseline rates in pregnant women. The actual rate of spontaneous fetal loss in the general pregnant population is unknown. Estimates have ranged 10–15%, but if early spontaneous abortions are taken into account, then values are 20–62% [306, 307]. However, a fetal loss of only 3% was reported [308, 309]. The fetal loss occurred in 4–61% in pregnant trauma patients, depending on mechanism and severity of injury [22, 34, 135, 303].

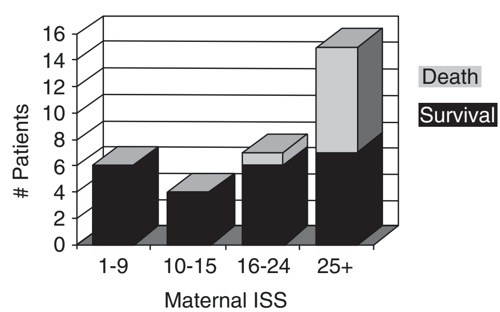

Fig. 10.31 Maternal mortality in 1966 by injury severity score (ISS) demonstrates that maternal injury adjusted mortality is compatible with established norms. Reproduced with permission from [277]

Fetal deaths depend on the type of trauma: MVAs (82%), gunshot wounds (6%), and falls (3%), with maternal death accounting for 11% of the fetal deaths [101]. Reports show that 10–30% of women are exposed to significant physical abuse during pregnancy, with an associated 5% rate of fetal death [34, 42, 244, 274]. Surgery for trauma has not been associated with an increased rate of fetal loss [121].

Evidence of disseminated intravascular coagulation requires immediate intervention because it is associated with poor fetal outcomes [15, 310] The maternal bicarbonate level at admission for blunt trauma was found to be predictive of fetal outcomes [35].

> The main cause of fetal death is maternal death.

The rate of fetal death from maternal trauma was calculated to be 2.3/100,000 live births [101], while after major maternal blunt trauma, it ranges 3.4–38.0% [4, 15, 22, 25, 33, 34, 46, 51, 277], mostly from placental abruption, maternal shock, and maternal death [4, 33–35, 101, 183, 277, 310]. Maternal shock due to major trauma has a 66–80% fetal mortality rate [303, 305]; therefore, an all-out effort must be made to sustain maternal life for the survival of the fetus. Significant maternal and fetal morbidity and mortality occur even with nonsevere injuries defined by ISS <9. Although 50 years ago higher scores were associated with worse outcomes (Fig. 10.31), even lower scores still have significantly elevated adverse fetal outcomes, therefore limiting their predictability in pregnant trauma patients [6]. Adverse pregnancy outcomes after minor trauma occur at a rate 1–5% [187]. Because more than 90% of injuries to pregnant women are the result of minor trauma, most pregnancy losses associated with trauma occur in cases of minor trauma [311]. Splenic and retroperitoneal injuries and hematomas are more frequent in pregnant patients with blunt abdominal trauma due to increased vascularity during pregnancy. Conversely, bowel injury is less frequent than in general population [7, 84].

Gestational age is the strongest predictor of fetal, neonatal, and infant death (Fig. 10.32) and less so the type, mechanism, or severity of the injury [6]. ISS of greater than 2 in the presence of a positive Kleihauer–Betke test result might be an effective predictor of adverse fetal outcome [312], but the value of ISS does not correlate with salvageable infant survival (Fig. 10.33). Fetal hemoglobin (HbF) is used to assess risk for adverse perinatal outcomes as a tool for identifying FMH, although there may be no correlation between HbF and the adverse fetal outcomes [313]. Elevated maternal serum AFP levels (>1000 ng/mL) after maternal trauma may predict adverse fetal outcomes despite the insignificant trauma and hemodynamic stability [313].

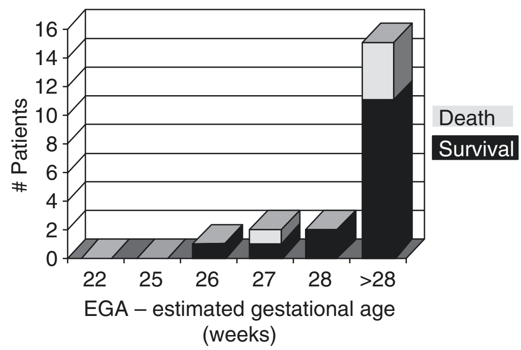

Fig. 10.32 Salvageable infant survival according to the gestational age. At gestational age less than 26 weeks, no infants survived. However, at a gestational age between 26 and 28 weeks, the survival rate increases to 80%. Reproduced with permission from [277]

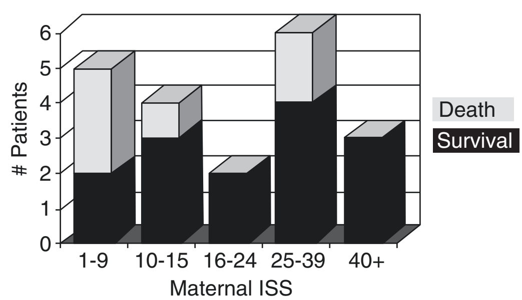

Fig. 10.33 Salvageable infant survival according to the maternal injury severity score (ISS). Infant death is distributed across the spectrum of severity and even the most injured mothers have good infant survival. Reproduced with permission from [277]

Maternal plasma bicarbonate level may be a predictor of outcome. Injured mothers with fetuses who survived had a mean plasma bicarbonate level of 20.3 ± 2.2 mEq/L compared with 16.4 ± 3.0 mEq/L in those with fetal loss [35].

10.3.8.2 Motor Vehicle Accidents

Perinatal Outcome

Although there have been dramatic improvements in the management and treatment of medical and obstetric conditions, fetal mortality, in general, has not been reduced because of a rise in nonobstetric causes (mostly MVAs). MVA in pregnancy is associated with a perinatal mortality rate of 3–6/100,000 live births in high-income countries, attributable in large part to placental abruption and uterine rupture [314]. MVAs alone in the United States result in 1300–3900 fetal losses per year [315]. Injury severity, associated abdominal and pelvic trauma, and gestational age have been shown in part to predict pregnancy outcomes after MVA [316]. The fetal/neonatal outcomes in the pregnancies that are delivered during the MVA admission, either spontaneously or in the context of a pregnancy complication such as a placental abruption, were poor; about a third ended in a perinatal death. Whereas some of these perinatal deaths would have been as a result of spontaneous preterm birth, the high rate of CS (61.1%) in the group who delivered during the MVA admission suggests a significant number underwent emergency delivery for maternal or fetal indications (e.g., placental abruption or abnormal fetal heart rate pattern on CTG). The low overall perinatal death rate of 1.4%, during the admission immediately following an MVA in pregnancy ≥20 weeks, is reassuring [5].

> For women who did not require delivery during the MVA admission, the rate of pregnancy and delivery complications, as well as perinatal deaths, was the same as for women who had not had an MVA during pregnancy [5].

In one study from Saudi Arabia, pregnancy loss was significantly greater in older, nonurban, employed women and in women with family income >6000 Saudi riyals (>1600 US$). It appears as a new prognostic factor, and higher family income could be a proxy for the presence of high-powered, luxury cars, which may encourage fast driving [317].

Maternal Outcome

The vast majority (>90%) of injuries to pregnant women resulting from MVA are minor [11, 50]. As compared with nonpregnant women, pregnant women admitted after an MVA suffered less severe injuries and consequently required fewer therapeutic interventions and a shorter hospital stay. The reasons are [11]:

- More likely to seek medical attention
- More likely to be admitted for observation and monitoring of the fetus
- MVA of a less severe nature
- More cautious and refrain from potentially life-threatening behaviors
- More likely to be wearing seat belts

More common observation is supported by a study conducted over a 4-year period, which found that of 318 pregnant trauma patients seen in an emergency department, only 8% would have been admitted in the absence of pregnancy [32].

> Pregnant women who had a collision-related MVA were at increased risk of requiring genitourinary surgery (OR 1.45). When restricted to women with a fracture, pregnant women were even more likely to require genitourinary surgery (OR 2.93), as well as require a blood transfusion (OR 1.21) [11].

The in-hospital mortality rate for pregnant women was less than that for their nonpregnant counterparts [11]. MVAs during pregnancy caused maternal mortality in 1.4/100,000 and maternal major injury in 23/100,000 pregnancies [314]. During the MVA admission, the majority of women who had no adverse out-

comes were admitted for 1 day and were discharged home undelivered. However, for those requiring delivery (≥20 weeks of gestation) during the admission, the rate of pregnancy complications was significantly higher than women who did not have an MVA during pregnancy. Over a quarter had a placental abruption, and over half delivered <37 weeks of gestation [5]. Elliott reported a maternal mortality rate of 21% after MVA [92]. The primary cause of death was uncontrollable hemorrhage, and the increased vascularity associated with pregnancy accounted for a large number of deaths due to hemorrhage.

Seat Belt Use

Studies conducted in the period 1989–2001, in Washington State (Table 10.11), have shown that pregnant women who were not tied with a seat belt have three times higher possibility of infant death and it is two times more likely to have complications during pregnancy than women who were tied at the time of accident [27].

Airbag Use

Studies show that activation of the airbag during traffic accidents caused a higher percentage of preterm childbirth and fetal mortality (Table 10.12). This indicates that the airbag negatively affects pregnant women during traffic accidents, but because of the large differences in the number of pregnant women (three times more when an airbag was not activated than it was) included in the research, the possibility of certain deviation is present which reduces differences in the impact of airbag to pregnant women. It is possible to conclude that the airbag has no negative impact on pregnant women during traffic accidents. It should be noted that, in this analysis, there was no available data on how many of the pregnant women involved in traffic accidents were tied with the safety belt. For vehicles that have airbags (mainly the front seats), in order to absorb the shock of activating the airbag in the body of pregnant women, the seat should be set back as much as possible, preferably a seat can be partially lowered.

Table 10.11 Types of injuries, by women hospitalized for a motor vehicle accident in Washington State, 1989–2001

Injury classification	Nonsevere injury (%)	Severe injury (%)
Fractures, dislocations, sprains	53.4	81.0
Intracranial injuries	9.7	25.0
Internal injury of chest	0	26.2
Internal injury of abdomen	2.9	20.2
Internal injury of pelvis	1.0	2.4
Open wound	17.5	41.7
Blood vessel injury	0.3	3.6
Superficial, contusion, crushing injury	53.4	26.2
Nerve and spinal cord injuries	0.3	1.2

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Table 10.12 Obstetrics and gynecology, Washington State (2002–2005): maternal and perinatal outcomes associated with airbag deployment among pregnant women in a motor vehicle accident

	Airbag (%)	No airbag (%)
Maternal outcome		
Preterm labor	15.7	10.3
Placental abruption	2.0	1.6
Labor induction	31.9	21.6
Cesarean delivery	26.8	24.1
Perinatal outcome		
Gestational age <37 week	11.1	10.0
Birth weight <2500 g	8.7	8.2
Small for gestational age	11.6	9.8
Meconium at delivery	6.5	5.7
Fetal distress	5.6	6.0
Respiratory distress	2.5	1.6
Fetal death	1.0	0.3

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Maternal Pelvic Trauma

Pelvic fractures can be particularly difficult to manage and life-threatening to the mother and the fetus and are the most common injury resulting in the fetal mortality rate of 13–67% [51, 149, 150, 153, 270, 304] with maternal mortality 7–29% [149, 153, 270]. These studies did not take into account possible additional, especially intra-abdominal injuries that could have an impact on the fetal mortality rate. If intraperitoneal hemorrhage is taken into account, the fetal mortality rate was 100%. Mortality rates of women who sustained pelvic trauma in pregnancy were not affected by the fracture classification (simple vs. complex), the fracture type (acetabular vs. pelvic), the trimester of pregnancy, or the decade studied [149].

10.3.8.3 Repeated Blunt Abdominal Trauma

The rate of emergency room visit for blunt abdominal trauma was 5.4/1000 deliveries encompassing 270 pregnant women with one or more noncatastrophic abdominal trauma during the second and third trimesters due to traffic accidents, falls, and assaults. There is only one study with an analysis of repeated blunt abdominal trauma with only 1.9% of women that sustained more than one blunt but direct blow to the abdomen due to falls during the second and third trimesters [319]. The time between the events ranged 1–4 weeks. The median hospitalization time per admission was 2 days, while all five patients together stayed in the hospital for 27 days in total during pregnancy. Extension to more than 24 h surveillance was exclusively due to preterm uterine contractions after the incident. Preterm contractions were noted in 60% (3/5) of patients, and one of which delivered at 34 weeks. Repeated blunt abdominal trauma occurs rarely in gestation and does not warrant clinical management except there are symptoms and signs of premature rupture of membranes, vaginal bleeding, placental abruption, or intrauterine growth changes. Restriction or antepartum death was encountered. The time between the last trauma and the delivery ranged 2–10 weeks. All patients delivered spontaneously. One patient, an epileptic woman, suffered from an increase of partial seizures with disturbances of motor function. Lack of compliance with the prescribed antiepileptic drug regimen could not be ruled out contributing to the rationale for the four extended hospital stays of that patient following the seizures. The Kleihauer–Betke test was positive in that patient only after multiple trauma events and negative in the rest of the patients including a patient who delivered preterm after two trauma events 1 week apart.

Repeated blunt abdominal trauma is rare but could induce preterm uterine contractions and labor. Delayed severe complications such as placental abruption have been reported as rather infrequent after noncatastrophic abdominal trauma due to fall [15, 107] and did not appear to be a more prominent issue after a second such event with a time lag of 1 week or more as in these series of five cases [319]. The Kleihauer–Betke test was not useful as a predictor of early or delayed complications after repeated blunt abdominal trauma but should be performed in all D-negative trauma patients to determine the appropriate dosage of D-immunoglobulin to be administered (300 mg/30 mL fetal blood transfused). After a visit, careful evaluation following repeated abdominal trauma and costly routine hospitalization for 24 h or more appears to be dispensable as in single-event cases [15]. Patients without premature uterine contractions or abdominal tenderness and with normal findings in the clinical evaluation, in the screening ultrasound, and in the continuous 4 h nonstress test may safely be sent home along with instructions for a proper follow-up in the outpatient clinic.

10.4 Penetrating Trauma

10.4.1 Incidence and Type

Of all abdominal traumas in pregnancy, penetrating trauma is present in 9–16% [320]. Of those, 73% were handgun-, 23% knife-, and 4% shotgun-related [320]. The incidence of maternal visceral injury with penetrating injuries is 19–38% [321]. Penetrating trauma in pregnancy has a different injury pattern to blunt trauma. The size of the uterus in pregnancy makes it the most likely organ to be injured, followed by the fetus and placenta. The gravid uterus may act to protect the abdominal viscera—only 18% of women

with gunshots sustain a visceral injury [322]. Buchsbaum explains this on the basis that the uterine muscle acts as a buffer to absorb missile energy and so prevent injury to the viscera beyond the uterus [323]. Although the gravid uterus protects other viscera, stabbings into the upper abdomen can cause serious injury, especially to compressed loops of bowel or to the overlying diaphragm. The latter is particularly dangerous in pregnancy if unrecognized, because of the possibility of subsequent bowel strangulation, which has much higher mortality rates in pregnancy (25–60%) than in the nonpregnant patient (16–20%) [180].

10.4.1.1 Gunshot Wounds to Uterus

The first report of a gunshot wound to the uterus is from the 1600s by Ambrose Pare, and the first recorded case of a gunshot wound of the pregnant uterus appeared in 1845 [324] and then by Verrier in 1888. A subsequent review, 10 years later, uncovered a total of 45 reports since 1845 [325]. In 1968, there were 16 additional cases, for a total of 61 in the world literature [48] and several more during the last several decades [326].

10.4.1.2 Stab Wounds to the Uterus

Reported instances of uterine stab wounds during pregnancy are even rarer. Review of the literature disclosed 33 cases of stab wounds of the uterus in pregnancy up to 2010 (Table 10.13). The typical patient stabbed in pregnancy is 18–28 years of age, almost always during the second half of pregnancy [327].

10.4.2 Clinical Presentation

Clinical presentation depends on the type of injury, number of wounds, extension of every wound, and number and extension of organs involved. During examination, entrance and exit wound(s), if exists, should be noted (Fig. 10.34). These can predict the bullet path and possible intra-abdominal injuries, but high-velocity projectiles are often unpredictable, and multiple wounds can exist concomitantly. If the uterus is damaged, continued or intermittent vaginal bleeding can be found [328]. Traumatic anhydramnios may be caused by a leak due to rupture of membranes with vaginal drainage or into the peritoneal cavity with penetrating wounds of the uterus.

10.4.2.1 Neurogenic Shock

It develops with the blockade of the sympathetic autonomic function by the cord injury whether blunt or more commonly penetrating abdominal trauma. It is characterized by a dominance of parasympathetic effects: hypotension and bradycardia with decreased cardiac output and warm dry skin leading to loss of heat and hypothermia, which can lead to further bradycardia and fetal distress. This clinical picture can obscure the typical signs of hypovolemia, such as tachycardia and cold clammy skin. Therefore, in any patient with abdominal trauma, neurologic status should be obtained to exclude spinal cord injury. Neurogenic shock can be anticipated to last from 1 to 3 weeks.

10.4.3 Diagnosis

Minor trauma (including minor bruising, lacerations, or contusions) may not be associated with an increased risk of placental abruption or adverse pregnancy outcomes when compared to the general pregnant population. Perhaps it is time to reevaluate the extensive evaluations that are often done since none of the objective measures are predictive of adverse outcomes. Specifically, KB tests, fibrinogen levels, and coagulation studies should not be performed in this patient population for the purposes of predicting placental abruption or adverse events [225].

> In the absence of maternal injury or any other clinically concerning signs, adopting a practice of a physical exam, brief fetal well-being assessment, and patient counseling on the warning signs and symptoms of placental abruption would be an appropriate strategy for women presenting after minor trauma at or beyond 24 gestational weeks [225].

Table 10.13 Reported cases of stab wounds to the pregnant uterus

Author	Year	Age	Gestational age at injury	Weapon	Mode of delivery	Time to delivery	Fetal injury	Perinatal outcome	Maternal wound	Maternal outcome
Guadagnini	1930	N/A	34	Dagger	Spontaneous vaginal	Same day	Right calf	Stillborn	Abdomen and uterus	Survived
Badia and Charlton	1940	20	28	Knife	Spontaneous vaginal	9 weeks	None	Living term	Abdomen and uterus	Survived
Flamrich	1941	N/A	N/A	Knife	Cesarean	Immediate	Wound to secretum	Living term	Abdomen and uterus	Survived
Steele	1941	N/A	N/A	Knife	Spontaneous vaginal	N/A	None	Living term	Abdomen, uterus, and bowel	Survived
Wright	1954	20	18	Knife	Spontaneous vaginal	19 weeks	None	Living term	Abdomen and uterus	Survived
Bolot	1957	27	Term	Knife	Spontaneous vaginal	N/A	None	Living term	Abdomen, uterus, left arm, bowel, and chest	Survived
Hammer	1960	25	32	Knife	Spontaneous vaginal	6 weeks	Right tight wound	Living term	Abdomen and uterus	Survived
Bochner	1961	21	29	Knife	Spontaneous vaginal	38 days	None	Stillborn	Left chest	Survived
Groplanov	1961	22	8 months	Shaving razor	Spontaneous vaginal	3 days	N/A	Neonatal death	Ten wounds of ileum and jejunum and uterus	Survived
Dyer and Barclay	1962	28	14 weeks	Knife	Hysterectomy	Immediate	N/A	Aborted	Abdomen, ileum performed, and uterus	Survived
Dyer and Barclay	1962	28	40 weeks	Knife	Cesarean	Immediate	Partially severed cord	Stillborn	Abdomen and uterus	Survived
Moss et al.	1962	N/A	16 weeks	Knife	Spontaneous vaginal	N/A	N/A	Aborted	Abdomen, uterus, and hematomas	Survived
Quast and Jordan	1964	N/A	6 months	Knife	Spontaneous vaginal	3 months	None	Survived	Abdomen and uterus	Survived
Gordon	1966	28	36 weeks	File blade	Cesarean	Immediate	Liver laceration and stomach perforation	Neonatal death on third day	Abdomen, uterus, and left chest	Survived
Shafian	1968	N/A	8 months	Knife	Spontaneous vaginal	N/A	None	Living term	Abdomen	Survived
Knapp and Drucker	1972	27	39 weeks	Knife	Cesarean	Immediate	Back and flank lacer	Survived	Abdomen, uterus, and liver laceration	Survived

(continued)

Table 10.13 (continued)

Author	Year	Age	Gestational age at injury	Weapon	Mode of delivery	Time to delivery	Fetal injury	Perinatal outcome	Maternal wound	Maternal outcome
McNabney and Smith	1973	23	N/A	N/A	Cesarean	Immediate	Liver and ileum convulsions	Survived	Abdomen and uterus	Survived
Malinovsky	1974	24	37 weeks	Knife	Cesarean	Immediate	None	Survived	Abdomen and uterus, sigmoid and mesentery	Survived
Amine	1976	24	8 months	Barbecue fork	Spontaneous vaginal	7 days	T6-T7 spine wounds	Survived	Abdomen and uterus	Survived
Golan et al.	1980	25	32 weeks	Knife	Spontaneous vaginal	3 days	None	Survived	Abdomen and uterus	Survived
Jacobson	1983	18	24	Knife	Cesarean	8 weeks	None	Survived	Abdomen and uterus	Survived
Jacobson	1983	25	38	Knife	Cesarean	Immediate	None	Survived	Chest, abdomen, and uterus	Survived
Degefu et al.	1986	20	38	Knife	Cesarean	Immediate	Both extreme	Stillborn	Abdomen and uterus	Survived
Sakala	1987	18	26 weeks	Knife	Cesarean	Immediate	Bowel evisceration and left tight wound	Stillborn	Abdomen and uterus	Survived
Raginia	1966	42	7 months	Knife	Spontaneous vaginal	5 days	Amniotic bag. Scapular region	Living term	Abdomen and uterus	Survived
Mukaramov and Mukaramova	1987	27	36	Knife	Spontaneous vaginal	Immediate	Lumbar region	Living term	Abdomen and uterus	Survived
Shapkin and Mel'nikov	1988	N/A	36–37	Knife	Cesarean	Immediate	Chest-pneumothorax 7 mL	Survived	Abdomen and uterus	Survived
Belousov and Romazova	1977	23	32	Knife	Cesarean	Immediate	Right lumbar region	Living term	Abdomen and uterus	Survived
Grubb	1991	26	30	Steak knife	Spontaneous vaginal	Immediate	Left parietal bone	Living term	Abdomen, uterus, and upper extremities	Survived
Schultz et al.	1993	19	29	Knife	Cesarean	Immediate	Right parietal region	Living term	Abdomen and uterus	Survived
Fleming et al.	2001	29	32	N/A	Cesarean	Immediate	Radial nerve injury, lower leg, and left anterolateral chest	Living term	Abdomen, uterus, and multiple stab wounds	Survived
Yildirim et al.	2003	27	34	Knife	Postmortem cesarean	Immediate	None	Survived	Abdomen, head, neck, thorax, and extremities	Dead
Gallo et al.	2008	20	30	Knife	Spontaneous vaginal	10 weeks	Right temporal region	Living term	Abdomen and uterus	Survived

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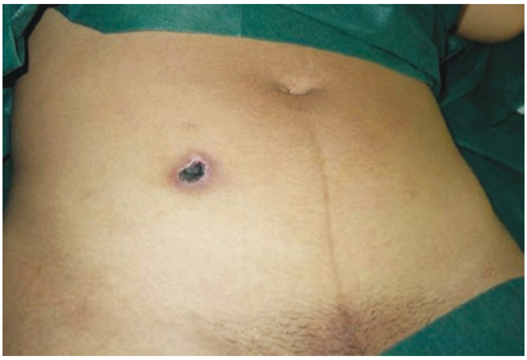

Fig. 10.34 Maternal entry gunshot wound healing. Reproduced with permission from [329]

10.4.3.1 Laboratory Findings

After serious trauma in a pregnant woman, complete blood count, blood type, and Rh status should be determined. Additional blood tests may be indicated in patients with more severe injuries.

Kleihauer–Betke Test

See Sect. 10.3.5.6.

Toxicology

In urban medical centers, 13% of pregnant patients admitted for trauma have detectable levels of alcohol, and 12% have positive toxicology screening results [51]. Therefore, alcohol levels and toxicology should be obtained during diagnostic workup.

10.4.3.2 Radiography

Fetal Radiation Exposure

Patients and physicians commonly are concerned about fetal exposure to radiation, but adverse effects are unlikely at less than 5–10 radiation absorbed doses (rads) [121, 239]. Less than 1% of trauma patients are exposed to more than 3 rads (Table 10.14) [32, 121, 220]. However, the risk to the fetus of a 1 rad exposure, approximately 0.003%, is >1000 times smaller than the spontaneous risks of malformations, abortions, or genetic disease. Intrauterine exposure to 10 rad does not appear to cause a significant increase in congenital malformations, intrauterine growth retardation, or miscarriage but is associated with a small increase in the number of childhood cancers. Poor growth, mental retardation, central nervous system defects, and microcephaly are the most common adverse events associated with extremely large doses of fetal radiation [239]. The relative risk (RR) of childhood cancers is greatest when a fetus is exposed to radiation in the first trimester (RR 3.19) and is especially high when exposure occurs before 8 weeks of gestation (RR 4.60) [220]. When the results of several studies were combined, the overall RR of in utero radiation was not statistically different from that of the general population [220]. After 15 weeks of gestation, fetuses are unlikely to be affected by radiation [220]. Fetal doses from identical procedures vary among pregnant women and are lower in obese women [330].

Intravenous Iodinated Contrast

Intravenous iodinated contrast crosses the placenta and is therefore classified as a FDA category B. Known risk is free iodine uptake by the fetal thyroid gland early in pregnancy, with the potential risk of inducing a hypothyroid state. Animal studies with intravenous iodinated contrast have shown no fetal risk, but no controlled studies on pregnant

Table 10.14 Radiation exposure for the unshielded uterus in various imaging studies

Imaging study	Uterine radiation dose (rad)
Plain film radiography	
Abdomen (AP)	0.133–0.92
Abdomen (PA)	0.064–0.33
Cervical spine	Undetectable
Chest (AP)	0.0003–0.0043
Chest (PA)	<0.001
Femur (AP)	0.0016–0.012
Hip (AP)	0.01–0.21
Pelvis (AP)	0.142–2.2 (mean 0.2)
Full spine (AP)	0.154–0.527
Lumbar spine (AP)	0.031–4.0
Thoracic spine (AP)	<0.001
Computed tomography	
Upper abdomen	3.0–3.5
Entire abdomen	2.8–4.6
Head	<0.05
Pelvis	1.95–5.0
Thorax	0.01–0.59

women have been performed, and theoretic risks remain [240].

Plain Abdominal X-Ray

Roentgenogram of the abdomen can show pneumoperitoneum if the shallow viscera are injured through the visceral wall. Also, bullet or fragments of the bullet (Figs. 10.35 and 10.36) can be found.

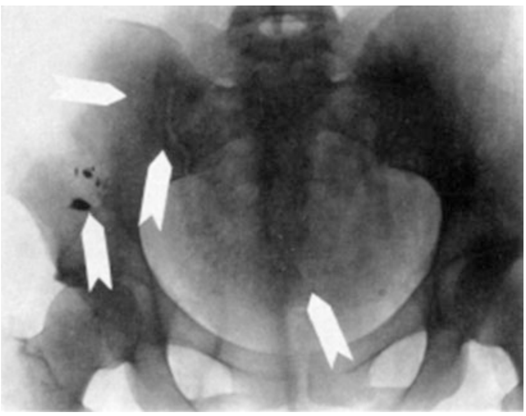

Fig. 10.35 A small fetus lying transversely across the pelvis and metallic fragments adjacent to the right iliac bone. Reproduced with permission from [328]

Fig. 10.36 Bullet inside the uterine cavity and the fetal head in vertex position. Reproduced with permission from [329]

10.4.3.3 Transabdominal Ultrasound

Maternal Status

Ultrasonography misses 50–80% of placental abruptions [33, 59, 183] but rapidly and safely determines FHT, placental location, gestational age, and amniotic fluid index [15]. Ultrasound examination is particularly helpful with maternal tachycardia, when the fetal and maternal heart rates may be difficult to distinguish with Doppler. Based on limited data, most obstetric ultrasonography results that are obtained after trauma are normal [15, 32, 46, 59, 166]. Few fetuses survive when ultrasonography detects evidence of fetal trauma (Fig. 10.37a) [15, 32, 46, 59, 166]. The benefit of a biophysical profile after trauma is unknown [166]. The accuracy of ultrasonography greatly depends on operator experience and maternal body habitus. Maternal pulsation can mimic fetal bradycardia or cause fetal movement, leading to unnecessary emergency deliveries in cases of fetal demise. Ultrasonography commonly is used to reassure the mother after noncatastrophic trauma, but this practice has not been studied.

Fetal Status

Doppler flow measurements of the umbilical artery may reveal high placental resistance associated with intrauterine growth retardation [331]. Oligo- or anhydramnios in this setting would raise suspicions of a diagnosis of placental insufficiency. All fetal organs should be examined and evaluated.

10.4.3.4 Abdominal CT

It is used when the ultrasound examination is not diagnostic and unequivocal. The risk and benefits should be weighed on every pregnant patient. Sometimes abdominal ultrasound shows free intraperitoneal fluid without obvious cause, and if the primary cause of the FF dictates the indication for the operation, CT is performed (Fig. 10.37b, c).

10.4.3.5 Peritoneal Lavage

If needed, open diagnostic peritoneal lavage, in which the peritoneum is visualized directly, or fistulogram is safe and accurate in pregnant women and was previously used more in the

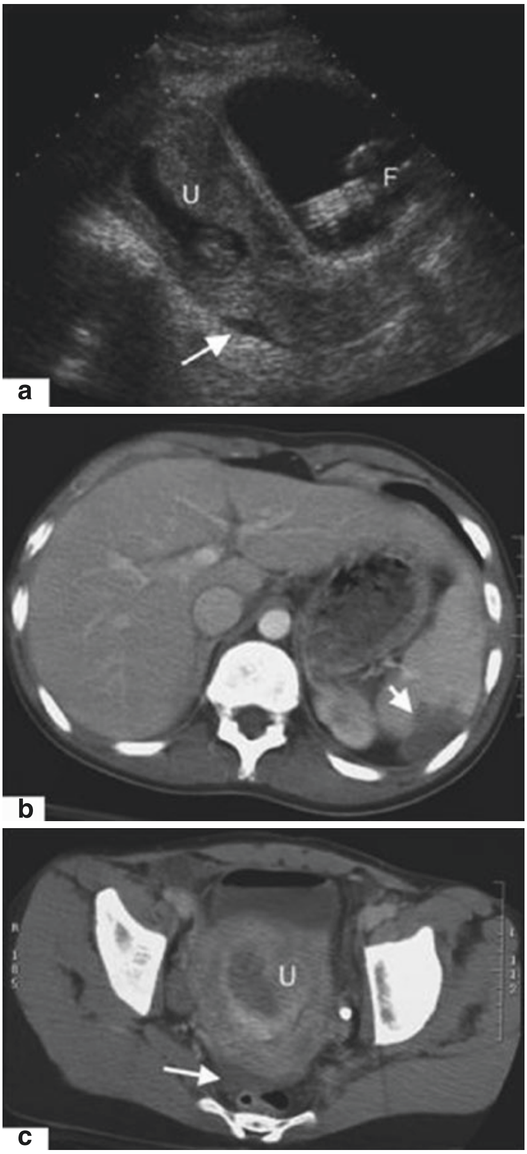

Fig. 10.37 The first-trimester high-speed motor vehicle accident that resulted in splenic laceration managed without intervention. (**a**) Longitudinal US image of the pelvis shows free fluid (*arrow*) in a cul-de-sac and an intrauterine (*U*) pregnancy. A Foley catheter (*F*) is present within the bladder. (**b**) Transverse helical CT scan of the abdomen shows laceration (*arrow*) in the posterior aspect of spleen but no substantial free fluid. (**c**) Transverse CT scan of pelvis shows an enlarged uterus (*U*) with gestational sac and free fluid (*arrow*) in the cul-de-sac. Reproduced with permission from [242]

conservative management of stable lower abdominal penetrating injury during pregnancy before the era of modern imaging techniques [17, 34, 84, 121, 332]. The complete diagnostic algorithm is presented in Fig. 10.38.

10.4.4 Treatment

10.4.4.1 Perioperative Management

Liberal administration of oxygen and fluids when the bicarbonate level is low improves tissue perfusion and fetal oxygenation [34, 35]. For other details, see Sect. 10.1.6 and Chap. 21.

Tetanus Prophylaxis

Tetanus is a rare, potentially fatal disease caused by the anaerobe *Clostridium tetani*. Wounds that are crushed, devitalized, or contaminated with dirt or rust are considered to be tetanus prone. Open fractures, punctures, and abscesses are also associated, but the severity of the wound does not determine the risk. All wounds should be cleaned and debrided if necessary. Tetanus toxoid should be given if the last booster was more than 10 years prior. If a vaccination history is unknown, tetanus toxoid can be considered when convenient. If the last immunization was >10 years ago, then tetanus immune globulin should be given. The tetanus toxoid dose is 5 IU IM, while tetanus immune globulin prophylaxis dosing is 250 or 500 units IM (in opposite extremity to tetanus toxoid) [121].

Rho(D) Immune Globulin

See Sect. 10.3.5.6.

Spinal Cord Injury

Gunshot wounds to pregnant women, especially when multiple, can result in acute spinal cord injury in addition to penetrating abdominal trauma. A number of issues are relevant to the management of the pregnant patient with spinal cord injury: (1) immediate measures, (2) neurogenic shock, (3) anesthetic aspects (see Chap. 21), and (4) the labor management if the fetus survived.

Immediate Measures

General resuscitation measures included intravascular volume assessment and maintenance, stabilization of the neck, and airway maintenance (by the jaw thrust technique rather than the head

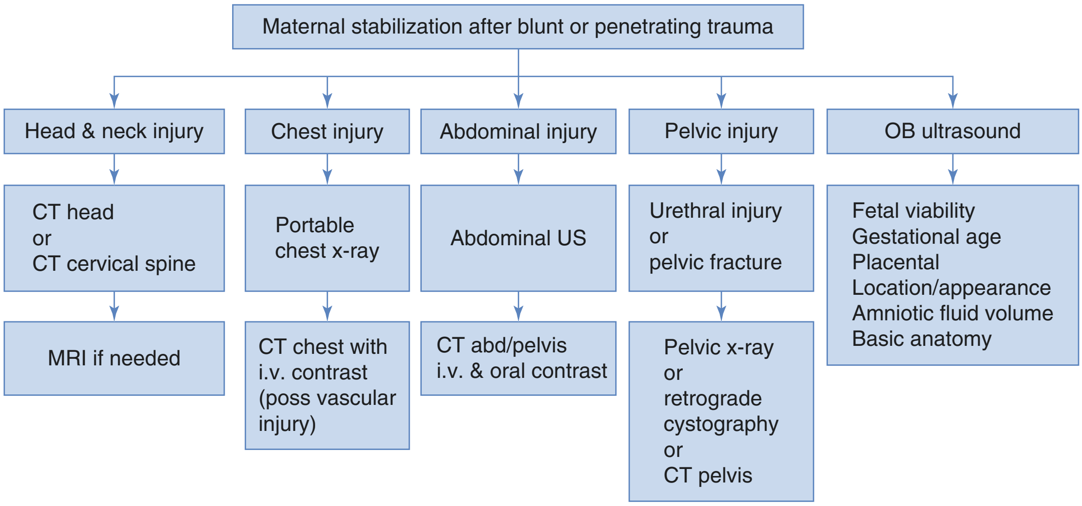

Fig. 10.38 Diagnostic imaging options for maternal blunt and penetrating trauma patients. US – ultrasound, CT – computed tomography, MRI – magnetic resonance imaging, OB – obstetric. Reproduced with permission from [240]

tilt/chin lift maneuver). Nasal intubation may be required if in need of assisted ventilation (*American College of Surgeons*, Committee on Trauma, 1993); electronic fetal heart monitoring provides an excellent means of assessing maternal hemodynamic status as well as fetal well-being. In cases of multiple injuries, it is prudent to rule out internal hemorrhage by peritoneal lavage with an open technique in late pregnancy or by means of an angiogram. The peripheral neurological deficit could be due to compression of the spinal cord by the edema or partial/complete transection. Administration of intravenous methylprednisolone within 8 h of the injury is a bolus of 30 mg/kg followed by 5.4 mg/kg for 23 h. This is associated with significant improvement in motor and sensory function 6 months after the insult [333].

Neurogenic Shock

Clinical presentation of neurogenic shock due to acute spinal cord injury is presented in Sect. 10.3.2.1. Management includes fluid replacement guided by central vascular monitoring and the use of positive inotropic agents such as dopamine and dobutamine (1–5 mg/kg/min) to enhance cardiac output, perfusion pressure, and renal perfusion. There is animal evidence of adverse effects of these drugs on the fetus, but in previous reports, these were not observed in humans with long-term use [334, 335]. Pulmonary complications of the involvement of the chest musculature by the neurological deficit are due to the restrictive effect of the pregnant uterus on the diaphragm and inadequate secretion clearance, iatrogenic pulmonary edema, malnutrition-related hypoproteinemia, and prolonged periods of hypotension that can all lead to the development of pulmonary stasis, infection, and ARDS [335].

Pneumothorax/Hemothorax

> If a thoracostomy tube is indicated, it should be placed one to two intercostal spaces above usual fifth intercostal space landmark to avoid abdominal placement [23].

10.4.4.2 Gunshot Wounds

Historical Perspective

Proposals for the management of such patients vary widely. In 1941, Bost indicated that the uterus should be emptied by CS, at almost any stage of pregnancy [336]. Eckerling and Teaff in 1950 stated categorically that the injured gravid

uterus must be emptied by CS, irrespective of the viability of the fetus, and particularly if the injured woman was in labor [337]. Their rationale was to avert the possibility of a ruptured uterus with labor and also to spare the injured patients of the additional heavy physical strain of labor and delivery, during the early postoperative period.

Conservative Treatment

Traditionally the presence of penetrating abdominal trauma necessitates surgical exploration. The practice of mandatory exploration was derived from military experience during World War II. Mandatory explorative laparotomy for all gunshot wounds to the abdomen in general population has been challenged first by Shaftan in 1960 with the selective surgical management of civilian injuries [338]. Consequently, the nonoperative approach has been neither universally accepted nor uniformly applied. The reappraisal in 1980 by Iliya et al. with respect to the applicability of selective exploration to pregnant women had little effect as well [339]. Accumulating data suggests a more selective approach [84, 326, 332, 340], but high-velocity gunshot wounds to the abdomen universally require exploratory laparotomy, given the high likelihood of intra-abdominal injury to the mother.

The nonoperative management of pregnant women with penetrating injuries to the abdomen may be applicable when the entry wound is below the uterine fundus [326, 339, 340]. Another reason is that in upper abdominal wounds, diaphragmatic lacerations must be ruled out [332]. By displacing the bowel superiorly and posteriorly, pregnancy markedly reduces the risk of bowel injury in the lower abdomen. However, careful patient selection is critical to the success of any suggested nonoperative management.

Selective laparotomy may, therefore, be contemplated in a pregnant woman with stable vital signs when the entry site is anterior and subfundal and when imaging techniques demonstrate that the missile has not crossed the posterior uterine wall. Iliya et al. [339] found a low incidence of life-threatening injury in pregnant patients and proposed the following criteria for conservative management:

- A fetus is dead
- Entrance wound is below the level of the fundus
- The bullet is radiographically shown to be in the uterus
- Maternal evaluation is reassuring
- Hematuria or rectorrhagia must be absent

The patient should receive adequate antibiotic coverage to prevent streptococcal bacteremia and/or clostridial myositis. Maternal surveillance requires intensive care unit monitoring, close nursing care, and repeated physician examinations, in addition to continuous fetal monitoring.

The nonoperative management of pregnant women exposed to trauma should be based on a complete understanding of the various physiologic and anatomical alterations during pregnancy. As a result of maternal physiologic hypervolemia, the pregnant woman can tolerate excessive blood loss before significant deterioration in her vital signs becomes evident. Thus, the slightest change in vital signs may indicate impending fulminant hemodynamic decompensation. Because of the potential for the supine hypotensive syndrome, the pregnant woman should be maintained in the left decubitus position during observation. On the other hand, because the uterus is not a vital organ, maternal hemodynamic stability is maintained at the expense of uterine perfusion. As a result, the fetal circulation may suffer long before the maternal circulation, and therefore late-onset fetal distress may be the earliest sign of maternal decompensation [323].

Medications

Regular contractions may signify placental abruption. Administration of tocolytics could compromise the fetus by delaying the diagnosis of placental abruption and consequently delaying delivery [Evidence level B] [59, 166].

Surgical Treatment

Kobak and Hurwitz recommended that all patients should be subjected to immediate

laparotomy as in the case of any patient with a gunshot wound to the abdomen [341]. Because of the anatomical alterations caused by the enlarging uterus, the pregnant woman appears to respond differently to abdominal trauma than the nonpregnant woman. In view of the space it occupies in the abdominal cavity, the gravid uterus plays the role of a maternal shield, protecting more vital maternal structures from injury. As a result, the incidence of visceral injuries in pregnant women with penetrating abdominal trauma is 16–38% [321], significantly lower than that in the general population, where it is 80–90% with anterior abdominal gunshot wounds and may exceed 95% with evidence of peritoneal penetration [342]. Because the mortality rate is proportional to the number of organs involved, the absence of maternal death among more than 100 pregnant patients with gunshot abdominal wounds reported after 1912 [343] clearly indicates the protective effect of the gravid uterus during pregnancy. It should be stressed that routine emergency laparotomy in general population may be associated with morbidity of 8–33% [344, 345]. Morbidity is mostly due to pulmonary complications, wound infection and dehiscence, small-bowel obstruction, and iatrogenic complications. The effects may be accentuated in the pregnant woman, as physiologic ileus and diminished gastric emptying increase the risk of pulmonary complications secondary to lung aspiration during unplanned emergency surgery. In addition, in advanced pregnancy, laparotomy wound can have a negative impact on the process of vaginal labor and also increase the possibility of a postoperative hernia.

The proposed signs for surgical intervention in general population included peritoneal irritation, a positive abdominal tap, persistent unexplained shock, and the ancillary signs of radiologically demonstrable free air, hematemesis, or rectorrhagia. With this suggested approach, it became increasingly obvious that about 12–40% of laparotomies performed for penetrating abdominal trauma were nontherapeutic and could be avoided if properly identified [262, 338].

Metal parts should be handled with plastic gloves and removed by forceps wrapped with gauze bandages as not preventing ballistic investigation due to additional marks and deformation of the metal.

While exploration is the management of choice in bullet wounds of the abdomen, CS is not mandatory, and indications for emergency CS are [346]:

- Surgical
- Pregnant uterus mechanically limits exploration or surgical repair
- Fetal
- Hemorrhage
- Interference with the fetal–maternal exchange
- Infection

Since infants have been born alive with soft tissue and visceral injuries, the hazards of prematurity must be weighed against the potential benefits of operation to the injured premature infant delivered by CS. When fetal weight approaches 2500 g, these hazards are greatly diminished. Vaginal delivery, even in the immediate postoperative period, has been shown to have no deleterious effect on the mother [337, 341, 347].

The subsequent treatment depends upon several factors. If the fetus is dead or previable and the uterine damage is not extensive, the uterus may be sutured and a vaginal delivery allowed [325, 337, 341]. The uterus is capable of a satisfactory, normal labor if the wound is small and well repaired, without danger of rupturing. In view of its inherent elasticity, the uterine muscular wall is relatively resistant to the cavitation and stretching produced by missiles, making damage minimal and debridement unnecessary [348]. The previous practice of mandatory debridement of military wounds was based on the observation that it reduced the risks of streptococcal bacteremia and clostridial myositis. However, with the introduction of antibiotics, this previously pressing need has been eliminated [349]. Extensive uterine damage or uncontrollable hemorrhage is an indication for CS (Fig. 10.39) and hysterectomy if the uterus is severely damaged or bleeding uncontrollable. Bowel perforation at that time did not carry higher mortality because all patients underwent laparotomy and all bowel lesions were repaired.

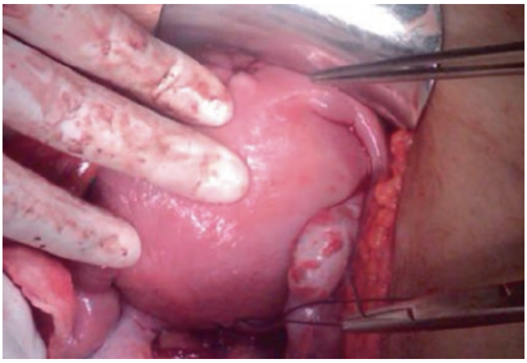

Fig. 10.39 The surgical instruments point the right anterolateral penetrating wound and the left posterolateral exit gunshot wound of the uterus. The bullet went through fetal head and thorax resulting in fetal death (see Fig. 10.42). Reproduced with permission from [350]

Fetal Gunshot Wound Characteristics

The fetal gunshot wounds do not have the characteristic features of entrance and exit gunshot wounds. Typical entrance gunshot wounds consist of circular perforations with marginal collars of abrasion, and typical exit gunshot wounds consist of slit-like to roughly circular perforations without margins of abrasion. The fetal gunshot wounds are atypical, and they do not clearly demonstrate the direction of fire. Catanese and Gilmore postulate that there are at least three factors that cause unusual gunshot wound characteristics in the fetus [351]:

- The presence of interposed targets
- Shoring of the fetus against itself and the uterine walls
- The composition of fetal skin

When bullets pass through interposed targets, the ballistic stability of the projectile is altered. An interposed target is any structure or material that a bullet passes through before entering a body, including windows, cars, layers of clothing, or other persons. In the case of a fetus that is injured by gunfire, the maternal body, the uterine walls, and the amniotic fluid all serve as intermediate targets which can alter ballistic stability. After passing through an interposed target, a bullet will enter the second target with an altered trajectory, which may create an atypical entrance wound. Also, the bullet can drag portions of the interposed target, such as pieces of bone or glass along with it, which can further alter the entrance wound. Atypical injuries are known to occur as a result of the passage of projectiles through an interposed target [352].

At term, the proportion of fetal tissue to the amniotic fluid is increased, and many of the fetal body parts are in contact with each other and the uterus. Shored entrance and exit wounds are wounds that occur when the skin through which a bullet enters or exits is pressed against a firm surface. When an exit wound is shored, the skin may show an irregular margin of abrasion as the elastic skin is stretched by the exiting bullet and rubbed against the shoring surface. If an entrance wound is shored, it is less likely to show a uniform margin of abrasion, and the pattern of injury will depend on the nature of the surface in contact with the skin [353]. One example of a shored entrance wound occurs when a bullet perforates an extremity and then reenters the trunk or another body part. In such a case, the skin at the reentry site is in contact with the exit wound on the shoring extremity, commonly producing an irregular wound with an atypical margin of abrasion.

Fetal skin differs from the skin of an adult or even the skin of a child. The composition of fetal skin depends on the gestational age of the fetus, as the morphogenesis of the appendages and the expression of the skin components are a sequential process. The fetal epidermis is covered by a layer called the periderm, which is a simple epithelial layer that has many blebs and microvilli, creating a large surface area that is exposed to the fluid in the amniotic cavity. The periderm persists throughout gestation and modulates the interaction of fetal skin with amniotic fluid components, including steroids. Although it is not known which cell receptors are used, it is known that steroids in the amniotic fluid affect both the water transport function of and the types of keratin expressed in fetal skin and that fetal skin has a greater water content than adult skin [354]. A more hydrated skin is softer and would then present less resistance to a projectile. This could

lessen the stretching caused by an entering or exiting projectile, causing an altered margin of abrasion or an atypical exit wound. At term, the collagens in the fetal skin are the same types that exist in adult skin, and they assume an adult configuration, but the relative amounts of collagen types differ. The predominant collagen in the adult skin is type I, which is a thick, fibrous collagen, and the predominant collagen in the fetal skin is type III, which is a fibrillary, interstitial type of collagen. In adults, type III collagen is restricted to the basement membranes and the perivascular areas [354]. This difference in collagen types may affect the strength of the skin and its resistance to the shearing forces caused by the velocity of a projectile.

Obstetric Management

Labor, whether spontaneous or induced, is almost always well tolerated by wounded patients [329]. On the other hand, if the fetus is viable (i.e., ≥28 weeks or ≥1000 g) and alive, immediate abdominal delivery is the treatment of choice [341, 347, 355]. Goff and Muntz favor prompt CS delivery of viable fetuses that survive the initial injury after maternal stabilization, with the aim of reducing the risk of delayed intrauterine death from occult trauma to the fetus or placental bed [356]. Browns et al. suggest that CS is absolutely indicated if the fetus is alive and near term, if the diagnosis of placenta hemorrhage is made or suspected, and if maternal injury necessitates laparotomy [357]. If there is an indication for CS, the baby should also be examined and all injuries noted (Figs. 10.40 and 10.41).

Fig. 10.40 Newborn with superficial wound 8 cm long over the left scapula. The extremities of the wound were healed, but its central portion was open for a distance of about 2.5 cm and was filled with healthy granulation tissue. There was no evidence of skeletal injury. Reproduced with permission from [328]

Fig. 10.41 Superficial wounds on baby's left scapular area and left shoulder (*arrows*). Reproduced with permission from [329]

Fig. 10.42 The photograph shows the lethal penetrating hole in the fetal face and an exit hole in the fetal thorax. Reproduced with permission from [350]

If there is no maternal indication for laparotomy, the preterm delivery of a live fetus with no evidence of acute distress or injuries may expose it unduly to the risks and complications of prematurity. Ultrasonography may be helpful in evaluating fetal well-being and determining the need for immediate delivery [32]. If there is a maternal indication for laparotomy with significant damage to the uterus, CS (with hysterectomy) is recommended because probably fetal death (Fig. 10.42) or significant fetal injuries are present.

Spinal Cord Injury

These patients may have painless contractions and painless cervical dilatation which, if missed, may result in an unattended delivery

and the occurrence of autonomic hyperreflexia. The patient should be taught self-monitoring for contractions by palpation where possible; regular tocodynamometry and periodic cervical examinations are an integral part of the management.

Labor is usually rapid and often painless. The use of forceps to shorten the second stage and thus decrease the risk of autonomic hyperreflexia has been advocated [358].

Mode of delivery is influenced by the usual obstetric factors, the site and stability of the lesion, the presence or absence of pelvic fractures, and the impact of pregnancy on appropriate monitoring and care.

There has been no reported increased incidence of third-stage problems or postpartum hemorrhage. Anemia, poor tissue perfusion, and lack of sensation may contribute to an increased incidence of perineal or ischial abscesses [358].

10.4.4.3 Stab Wounds

Conservative Management

Most stab wounds without maternal hard signs, such as hypotension, evisceration, hemorrhage, or peritonitis, can be managed nonoperatively (Fig. 10.43). If the patient is hemodynamically stable, every wound should be explored in local anesthesia. In nonpregnant women, if the fascia

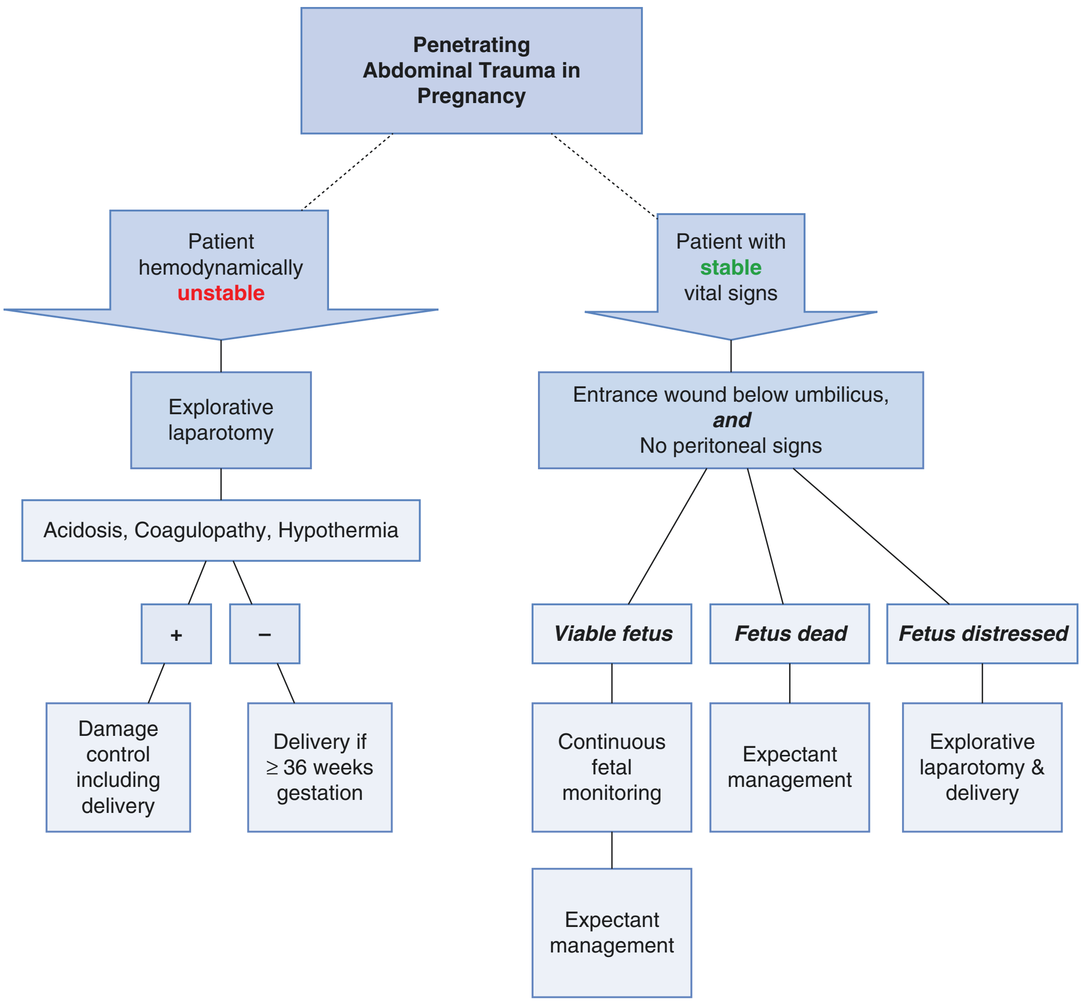

Fig. 10.43 Treatment algorithm for *penetrating* abdominal trauma in pregnancy. Reproduced from [360] under the CC Attribution License

is severed or the finger can reach intraperitoneal space, exploration is indicated. Diagnostic laparoscopy or laparotomy is then made to diagnose potential intra-abdominal injury resulting from a low-velocity stab wound. Otherwise, only primary wound care is indicated. This approach is not universal in pregnancy, and the decision to proceed with surgical exploration is a function of the location of the injury, uterine size, and maternal and fetal vital signs [359]. If conservative/observational treatment is initiated, serial examinations of the mother and continuous external fetal monitoring are mandatory (see Sect. Obstetric Management).

Obstetric Management

Fetal trauma after stabbing injuries to the uterine cavity occurred in 93%, and 47% of fetuses died after stabbings to the maternal abdomen [332]. Current fetal survival is 72.7% [327].

> The third-trimester fetuses subjected to stabbing injuries should be delivered promptly [361], while injuries known to penetrate the uterus may be managed with the fetus left in utero if there is no evidence of fetal distress or amnionitis [327].

Although perforation of the uterus near term may require CS for fetal indications, in most cases conservative management of uterine wounds is acceptable [48, 105]. This usually involves simple repair of uterine lacerations with subsequent vaginal delivery. Even when a penetrating injury has caused fetal death, the uterine wound should be repaired, with vaginal delivery later [184]. In spite of these advantages of vaginal delivery, one must be cognizant of the possibility of placental injury with abruption.

In the 1940s and 1950s, it was categorically stated that the injured gravid uterus must be emptied by CS, irrespective of the viability of the fetus [336, 337]. Fortunately, these recommendations are not valid today.

Brief observation (4–6 h external fetal monitoring) is indicated when:

> - Maternal trauma is minor
> - The mother is hemodynamically stable
> - Primary evaluation negative
> - FAST-US negative for intra-abdominal fluid
> - No obstetric complaints
> - <6 contractions per hour
> - Class I FHR pattern
> - Normal examination and laboratory data.

Prolonged observation (24–48 h EFM) is indicated when:

> - Multiple or severe maternal injuries
> - Mother hemodynamically unstable
> - Obstetric symptoms are present (bleeding, ROM)
> - >6 contractions per hour during first 4–6 h
> - Abnormal FHR pattern or deceleration on CTG
> - Abnormal examination (e.g., fundal tenderness)
> - Abnormal laboratory data (e.g., +KB, abnormal fibrinogen)

Surgical Treatment

Treatment algorithm for penetrating abdominal trauma is presented in Fig. 10.43. Surgical exploration for an abdominal penetrating wound is not an absolute indication for the removal of the fetus from an uninjured uterus. The performance of a CS significantly increases blood loss and operative time. The risk of precipitating labor after explorative laparotomy is negligible, if proper care is taken [340]. Emptying an uninjured uterus is justified only if the uterine size limits either adequate abdominal exploration or repair of extrauterine injuries or in the presence of nonreassuring fetal status. It should be stressed that CS may have beneficial effects on maternal resuscitation due to elimination of the low-resistance uteroplacental circulation [17,

49]. In patients with fetal death, it is advisable to afford delivery by induction of labor rather than uterine evacuation at the time of laparotomy [84, 332, 340]. In the rare occurrence of patients who present in the perimortem state with a viable fetus, perimortem CS should be considered (see Sect. 10.4.4.4).

10.4.4.4 Emergency Cesarean Section

CS should be done if:

- Maternal resuscitation fails/cardiac arrest
- The uterus interferes with the examination and repair of the maternal injuries
- A fetus is mature and is suspected of having direct injury
- Maternal shock
- Possible exsanguinations from any cause
- Irreparable uterine injury
- Fetal distress in a viable fetus
- Unstable thoracolumbar spine injury
- Pregnant near term

In the second- and third-trimester burn victims, delivery should be considered if affected total affected body surface area is >50% (see Sect. 10.3.5.1).

Emergency CS performed at >25 weeks of gestation for specific indications following trauma is associated with 45% fetal survival and 72% maternal survival [277].

Maternal Cardiac Arrest and Perimortem Cesarean Section

The difficulty in performing CPR in pregnant women in the third trimester is that the uterus in the supine position occludes the vena cava. CPR is described in detail in the Sect. 10.1.6. Restoration of both maternal and fetal circulation is the goal of adequate resuscitation. Maternal revival after delivery of the fetus has been reported in perimortem circumstances, presumably due to the relief of vena cava compression, or more effective CPR after pressure below the diaphragm is relieved, but this is rare. It is therefore suggested that there is no place for postmortem CS—only perimortem CS. Optimization of cardiac output and perfusion of the uterus via left thoracotomy and open cardiac massage along with perimortem CS should be considered. In cases of emergency center thoracotomy, recall that the aorta is often cross-clamped, further adding to the time of uterine hypoperfusion and decreasing the likelihood of a favorable outcome [24].

Delivery has also been reported to allow successful maternal resuscitation. Immediately after spontaneous delivery, cardiac output rises by 60–80% of prelabor values [81] and after CS by 30% of prelabor values [362]. The smaller increase associated with CS is due to anesthetic-induced hypotension and blood loss, which usually averages 1000 mL.

The decision to proceed with perimortem CS must be made quickly by the trauma or abdominal surgeon and obstetrician; hemostasis and antisepsis become secondary issues. Neonatologists must be available. Perimortem CS rarely is required [277] but is an ethically difficult decision for emergency medicine resuscitation teams. The procedure covers emergency delivery during the ongoing maternal CPR where the mother has no sign of recovery afterward with or without infant survival [363]. Maternal CPR must be continued until delivery is accomplished.

Historically, the operation was performed In Egypt as early as 3000 BC [364]. Sage Sustra, who practiced around 600 BC and is one of the founders of ancient Hindu medicine, referred to postmortem abdominal delivery in his medical treatise *Sustra Samhita* [365]. It is possible that in both Egypt and India this procedure was ordained by law [364]. Postmortem CS was spread with the Roman decree (*Lex Cesare,* or law of Caesar). The purpose of this ancient law was based on religious rituals to keep the fetus from being buried with the mother rather than attempts for survival of the newborn. According to the law of Caesar (decreet by Numa Pompilius), the unborn infants should be separated from their mothers' bodies after death. In 237 BC, the first reported infant who survived a postmortem CS was Scipio

Africanus, who subsequently became the Roman general who defeated Hannibal [366]. It was not until 1500 AD, when Jakob Nufer sectioned his own wife, that the operation was performed on a live woman with survival of both the mother and the infant [366]. In his book from 1545 [367], Charles Estienne (1504–1564) provided the first illustration demonstrating the procedure for a postmortem (cause unknown) CS to deliver a living neonate (Fig. 10.44).

The results of postmortem CS for all causes until recently were very poor. In the German duchy Kurhessen in 1848, there were 107 cases with no survivors [368]. In 1864, a physician collected and presented a series of 147 cases at the Berlin Obstetrical Society. Only three infants survived [369]. Katz et al. reviewed the literature from 1879 to 1985 and reported a total of 269 cases with 188 infants surviving. However, these authors cautioned that because of probable

Fig. 10.44 First known illustration of postmortem Cesarean section by Charles Estienne in 1545. Reproduced with permission from [367]

underreporting of unsuccessful cases, the true percentage of survivors is impossible to ascertain [368]. Katz et al. reported on the relation of infant survival to the time interval between maternal death and the delivery. In their review of cases from 1900 to 1985, there were 61 cases with neonatal survival and known time interval. Fifty-seven (93%) were born within 15 min, and only two had neurological damage, one mild and one severe. Seventy percent of the survivors were born within 5 min [368]. There are cases with live infants when postmortem CS was performed between 7 and 22 min after documented maternal cardiac arrest. Follow-up of infants demonstrated no evidence of neurologic damage [369, 370]. Therefore, emergency CS after 4 min of cardiopulmonary arrest increases the chances of fetal survival and aids to effective maternal resuscitation (Fig. 10.45) [121, 368].

The first modern approach to perimortem CS was reported by Katz et al. in 1986 [368]. Strong et al. in 1989 reported that about half of the perimortem CS in the literature had produced live infants, but the incidence of neurological sequel increases with increasing delays to delivery. The long-term survival rate of healthy infants was 15% [371]. Perimortem CS is an extremely emotional and often futile exercise and should only be considered in the emergency department when:

- Uterine size exceeds the umbilicus or gestation >24 weeks
- Evidence of fetal heart activity (Doppler or M-mode ultrasound)
- Unsuccessful maternal CPR <4–5 min (up to 15 min if fetal vital signs persist)

The appropriate incision for a perimortem CS is from the xiphoid to the symphysis pubis through all layers of the abdominal wall and peritoneum. When the uterus is identified, a vertical uterine incision is made, and if the placenta is anterior, it

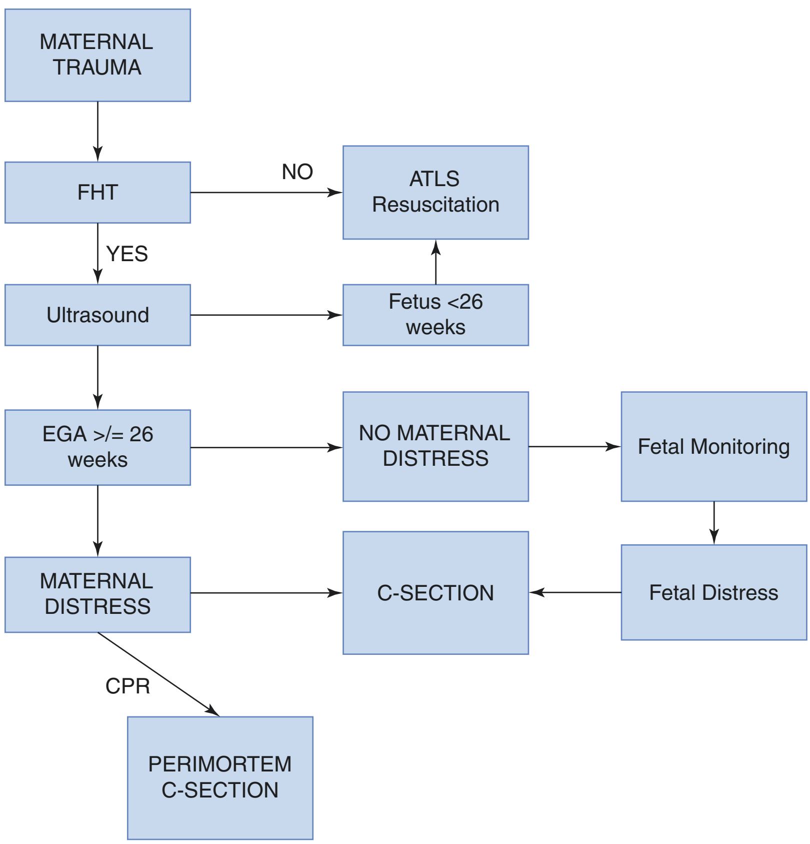

Fig. 10.45 Clinical algorithm for the emergency Cesarean section and perimortem Cesarean section. The pregnant trauma patient is assessed for fetal heart tone (*FHT*) and estimated gestational age (*EGA*). If FHT is present and EGA is ≥26 weeks, fetal monitoring is required. Fetal or maternal distress mandates emergency Cesarean section. Perimortem Cesarean section is performed if cardiopulmonary resuscitation is in progress. Reproduced with permission from [277]

should be incised as well. To deliver the infant, the gynecologist/surgeon opens the uterus, clamps and cuts the cord, and begins infant resuscitation. Maternal resuscitation should continue simultaneously, as there are reported cases of maternal survival after the delivery of the infant [372]. Before 23 weeks of gestational age, delivery of the fetus may not improve maternal venous return. Therefore, aggressive maternal resuscitation is the only indicated intervention [276].

Of infants delivered by this method in general, approximately 15% survive and are discharged from the hospital in good condition [366, 373, 374]. The survival of these infants depends on how soon they are extracted, their maturity, the duration and nature of the mother's illness, the performance of postmortem maternal CPR, and the availability of neonatal intensive care [375]. Although recent reviews conclude that despite being reports of 30 years supporting perimortem CS, they fall far from proving that it improves maternal and neonatal outcomes [376]. Of the 330 reported cases of postmortem CS during the eighteenth century, only seven living children were recovered. Then, in 1916, fetal survival of 42.3% was published [377].

Salvageable Infant

The most important finding is the definition of a subgroup of infants who are potentially salvageable. In this group of patients, defined by an estimated gestational age ≥26 weeks and the presence of FHTs, the survival rate is 75%. Survival is independent of maternal distress but clearly related to the presence of fetal monitoring and early recognition of fetal distress. There were no survivors in fetuses having no FHTs. This supports the premise that fetal viability is directly related to the presence or absence of FHTs on admission.

> The urgent Cesarean section is not considered as fetal heart sounds could not be heard during the initial evaluation of the mothers who died.

As such, the presence of FHTs is a simple, rapid, reproducible, and profoundly important marker of fetal viability. The recommendation is that the Doppler assessment of FHTs is a component of the primary survey performed on trauma patients during the third trimester of pregnancy. This should be accomplished simultaneously with the assessment of maternal circulatory integrity during the ABCs of the trauma resuscitation. If FHTs are absent, the pregnancy should be ignored and treatment directed solely at maternal survival. Survival of infants of 23–25 weeks of gestation increases with each additional week of gestation [378]. However, the overall neonatal survival rate for infants born during this early gestational period remains less than 40% [277]. Of those who survived, 6–40% have moderate to serious disabilities, and many have neurobehavioral dysfunction and poor spontaneous school performance [379].

As noted previously, high admission FHR values may be expected for patients arriving at the ED soon after the start of maternal hemorrhage. Furthermore, obstetric practice in the nontraumatic setting has documented baseline FHR to be less predictive of fetal stress than baseline variability and periodic change assessment of the FHR [380]. Lack of knowledge of baseline FHR prior to trauma and the wide variability (20 bpm) of FHR under normal physiological conditions [381] further degrade the predictive utility of admission FHRs. Although it is ideal to inform the prospective parents regarding fetal outcome and the financial and emotional consequences of profound prematurity, this is not possible in the trauma setting where the patients are often critically ill or sedated, families are unavailable, and the decision-making process is obscure. Consequently, it is recommended that fetal viability in the trauma patient should be defined at age 26 weeks. This recommendation changes the previous recommendations in the literature from 28 weeks, because up to 80% of infants with an estimated gestational age of 26–28 weeks could survive [277]. Even in the most profoundly injured mother, manifested by an ISS >25, fetal survival could be 78% [277]. This same critically ill population had a maternal survival rate of only 44%, illustrating the need for emergency CS at the first indication of fetal distress. Recognition of fetal distress is critical. In this study, fetal dis-

tress was defined as a FHR <100/min, prolonged deceleration for more than 60 s, or recurrent late decelerations. Although maternal survival in the presence of an ISS <16 was 100%, fetal survival was only 73% [277], supporting previous evidence that even minor maternal injury can result in fetal death [210]. Of more concern was the finding that 60% of these infant deaths occurred in mothers with minor injury and delayed CS in the presence of fetal distress. This may well represent delayed recognition of fetal distress or delayed CS in a misguided belief that the intrauterine environment is superior to delivery.

ACOG has published guidelines on performing CS for mothers in extremis following medical disasters, i.e., amniotic fluid embolism, cardiac arrest, etc. (www.acog.org). These could be extrapolated to similar physiological insults to a pregnant trauma patient. Fetal survival rates of 70% have been reported for fetuses of at least 25 weeks of gestation who are delivered within 5 min of maternal death [368]. Incidentally, these authors revisited their 1986 recommendations in 2005 and documented 38 cases of perimortem CS with all fetuses surviving initially but 4 dying of complications from prematurity and anoxia [376]. All mothers survived except for one, who died of complications of her amniotic fluid embolism.

10.4.5 Prognosis

10.4.5.1 Maternal Outcome

Gunshot Wounds

The maternal mortality rate from gunshot and stab injuries to the abdomen is less than that of nonpregnant women [84, 326, 332, 340, 356]. The gravid uterus during (late) pregnancy acts to shield other abdominal viscera as well as to displace and compress the small bowel. The uterus also diminishes the velocity of a missile and thereby decreases its ability to penetrate other organs. The musculature of the pregnant uterus is relatively dense, and most of the traumatic force is transmitted to the muscle. Moreover, the amniotic fluid and the fetus also contribute to slowing the bullet. Hence, injury to other organs is relatively rare [340].

The mortality rate of abdominal gunshot wounds in general population is proportional to the number of organs injured [382]. Associated injuries of gunshot wounds to the pregnant uterus occur in 24–38% [48, 325, 341]. Maternal mortality rate is 3.9–10.5% [305, 320, 383], but half of these were due to severe head injury [22, 135, 303, 305, 320, 383]. Thirty-three cases of gunshot wounds of the pregnant uterus during 1845–1954 were reported [341]. There were three maternal deaths, all of which occurred before 1912.

The penetrating trauma group has a longer hospital length of stay (7 ± 9 vs. 4 ± 8) compared to the blunt trauma group [320].

Stab Wounds

Stab wounds have a better maternal prognosis due to the absence of shock waves, the ability of visceral organs to slide away from the advancing knife blade, and the protective shield of the uterus. Up to 2010, maternal survival was almost 100%, and the only patient that died was due to associated 25 knife injuries in her head, neck, thorax, and extremities [327].

10.4.5.2 Fetal Outcome

There are several fetal factors that have an impact on fetal outcome (in addition to maternal factors and availability of tertiary center for high-risk neonates):

- The second trimester of pregnancy
- Multiple > single wounds
- Gunshot > stabbing wounds
- Thoracoabdominal wounds

Pregnancy loss was significantly greater in women in the second trimester of pregnancy compared to the first trimester. The second trimester represented the most vulnerable period for all types of fetal trauma because the gravid uterus ascends out of the bony pelvis in the cephalad direction to reach the level of the umbilicus by 24 weeks; here the gravid uterus may sustain direct traumatic injury. In the third trimester, the

fetus is well protected by the amniotic fluid [317]. However, in both gunshot and stab wounds, as pregnancy progresses, the fetus presents a larger target and is more likely to sustain an injury [84, 326, 332, 340, 356].

Fetal thoracoabdominal gunshot wounds 40 years ago had the mortality rate of almost 100% [323, 357].

The fetus has a worse prognosis than the mother, with an injury rate of 59–80% and a perinatal mortality rate of 40–71% [320, 383, 384]. The perinatal mortality during 1957–1967 was 71% [48], unchanged from the period 1845–1964 [325]. This is considerably higher than the 59% in the years after 1967 [48]. In the period 1845–1954, fetal mortality was 55% among those patients who were judged to have a viable fetus at the time of injury [341]. In the same period, the fetal mortality among those who had vaginal deliveries was 66%; among those who had abdominal deliveries, it was 46%.

With gunshot wounds, fetal injuries range 60–90%, and gunshot wounds commonly lead to fetal death, with an overall perinatal mortality of up to 70% [84, 323, 340, 385]. Perinatal mortality of viable fetuses up to 1972 was 59% [385]. A significant portion of fetal death in both stabbing and gunshot wounds is due to immaturity from ill-timed delivery. Up to 1977, fetal mortality was 78% if intrauterine gunshot wounding occurs preterm, but only 40% if the injury is incurred at term [357].

Previously fetal trauma after stabbing injuries to the uterine cavity occurred in 93% with a fetal mortality of 47% [332], while recent review found fetal mortality of 27.3% [327].

Maternal Injuries and the Risk of Birth Defects

Few studies have examined the association between maternal injuries and birth defects. Studies reported an increased incidence of birth defects among women who experienced “accidents” resulting in the damage/defects of the central nervous system, especially hydrocephaly [103, 386]. The results stratified by intention suggest that three of the associations observed when all injuries were considered, those for longitudinal limb deficiency, gastroschisis, and hypoplastic left heart syndrome, might be driven by intentionally inflicted injuries [28]. The majority of the intentional injuries are the result of intimate partner abuse, and these types of injuries could be more stressful for the mother [30]. Associations have been observed between maternal stress during pregnancy and several birth defects, including conotruncal heart defects, neural tube defects [100, 387], and orofacial clefts [100, 387]. Periconceptional injuries were associated with interrupted aortic arch type B, atrioventricular septal defect, pulmonary atresia, tricuspid atresia, hypoplastic left heart syndrome, anorectal atresia/stenosis, longitudinal limb deficiency, and gastroschisis. Associations with longitudinal limb deficiency, gastroschisis, and hypoplastic left heart syndrome were stronger for intentional injuries. This analysis was hypothesis generating, with many associations tested.

Although any maternal injury during pregnancy could be stressful for a woman, stress due to intimate partner violence could be both acute (during an attack) and chronic, from being in an abusive relationship. Intentional injuries are also related to many other factors that might cause or be related to other causes of birth defects. There is a higher prevalence of alcohol and cigarette use during pregnancy among women who reported an intentional injury [30]. Alcohol use and cigarette use during pregnancy are associated with increased risk for birth defects [388, 389].

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11 Miscellaneous Conditions

Abstract

This chapter summarizes many different conditions not summarized in other chapters. Although rare it includes several common causes of bleeding during pregnancy. These are spontaneous liver rupture, peptic ulcer bleeding which is extremely rare, and inferior epigastric artery bleeding. Bleeding from peptic ulcer and the inferior epigastric artery is commonly treated conservatively. On the contrary spontaneous liver rupture due to HELLP syndrome is a life-threatening condition with high maternal and fetal mortality. Only early recognition of underlying cause, before the rupture, or early surgical cessation of bleeding with the simultaneous Cesarean delivery of viable fetus contribute to improved maternal and fetal outcome. Additional conditions included are gastrointestinal–genital communications. In the nonpregnant population, these are rarely emergent conditions. In pregnancy, due to the communication with a gravid uterus and possibility of spreading an intra-amniotic infection, such communications have deleterious consequences to the fetus. Therefore, these conditions represent true emergency during pregnancy and should be treated surgically in consultation with an obstetrician if delivery is indicated.

11.1 Spontaneous Liver Rupture

Very exceptionally lesions of the liver are observed as the result of violent muscular exertion, as in the course of parturition or epileptic seizures. In such cases it is usually necessary to assume a diminished resistance of the organ as a necessary condition.

Allesandri, 1927.

11.1.1 Historical Perspective

Spontaneous rupture of the liver resulting from insignificant or no trauma has been noted in the literature for more than a century. The first known case was reported by Vesalius at some undetermined date. Andral, in 1829, sketchily reported two cases complicating lesions which may have been gummata or carcinomas. In many of the earliest cases, there is some possibility that gastric hemorrhage, secondary to liver disease, may have been mistaken for actual rupture of the liver. Thus, a case quoted in *Paris Medical*, in 1847, by Fauconneau and Dufresne, as reported by Latour, was undoubtedly such an instance. Abercrombie reported a case of ruptured liver complicating pregnancy in 1844 [1]. It was a case of a 35-year-old woman who, to obtain relief from "gastrodynia," took recourse to placing a silk

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_11

handkerchief around her body and pulling it tight to give her relief. On this occasion, a servant pulled the handkerchief so tightly that *it made me fear some injury under existing circumstances*. The author, therefore, begged for its removal and prescribed a draft composed of calcined magnesia, Liquor Opii Sedativus, Spt. ether, sulfur, and Aq. cinnamomi to be taken immediately and ordered hot fomentations to the epigastrium. By these means, the pain gradually abated. A few hours later, labor began and was soon followed by the successful breech delivery of the fetus. Some 50 min after the expulsion of the placenta, the patient collapsed. Hemorrhage was suspected, but there was no evidence of its coming from the birth canal. Several famous physicians and surgeons were called in consultation, but the patient died 26 h after delivery. A postmortem examination revealed about 2 lb of blood in the abdomen and two lacerated openings in the liver substance, about an inch apart. The liver itself presented a mottled appearance throughout and was unusually soft. Bleeding came from a torn branch of the portal vein. Abercrombie was of the opinion that the damage to the liver might have been caused by the tight bandaging but that hemorrhage did not occur until the pressure of the gravid uterus on the upper abdomen had been removed. He also put forward an alternative suggestion that hemorrhage took place in a liver that was already so diseased that it was readily injured by the muscular compressions of labor.

Devic and Beriel, in 1906, reviewed the literature of spontaneous rupture of the liver [2]. Two excellent reviews from 1938 and 1940 added important information [3, 4]. Spontaneous rupture of the liver is rare and exceptional. A number of causes for its occurrence have been described, and traumatic rupture is not a rarity. Allessandri stated: *Very exceptionally lesions of the liver are observed as the result of violent muscular exertion*, *as in the course of parturition or epileptic seizures. In such cases, it is usually necessary to assume a diminished resistance of the organ as a necessary condition* [5]. A case by Rademaker, although complicating pregnancy, was not in labor [6]. Rademaker collected 28 cases in the general population and found that causes other than violent muscular effort are multiple. Some associated disease or even minor trauma was present in all but three cases of 28 collected. It is no wonder that Sciacca came to the conclusion that when rupture of the liver occurs with minimal cause, the parenchyma is probably not normal [7].

Alessandri (quoted by Rademaker [6]), writing on this subject, agrees that rupture of the liver may occur as the result of violent muscular activity during parturition or during epileptic seizures, but he gives no case report or reference to support his views. Rademaker submits the interesting suggestion that sudden death during eclampsia may sometimes be due to a ruptured liver [6]. It is doubtful, however, whether this speculation can be sustained, for, although scattered areas of necrosis and small subcapsular hemorrhages are not infrequently found in eclampsia, severe hemorrhages of the liver are not a feature of this disease. Another case was by Links in 1946 during the fourth month of pregnancy. The cause of the liver damage was obscure, but Links suggests that it may have been due to transient hypertension. Burton-Brown and Shepherd described a case 17 h after parturition [8]. The injury was the result of trauma produced by violent contraction of the diaphragm and abdominal muscles during labor. But it is interesting to note that there was also an element of toxemia, evidenced by the raised blood pressure and albuminuria.

11.1.2 Incidence

Spontaneous liver hemorrhage during pregnancy is uncommon and mostly associated with preeclampsia, eclampsia, or an HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) [9, 10]. In 1982, Weinstein introduced the acronym HELLP to describe a syndrome observed in severe preeclampsia consisting of hemolysis, elevated liver function tests, and low platelet counts [11]. The incidence of subcapsular hepatic hematoma formation with capsular rupture in pregnancies varies from 1/30,863 to 1/250,000 deliveries [12–14]. The incidence of hepatic rupture in patients with HELLP syndrome is 0.4–1.8% [15, 16]. However, a spontaneous

hepatic rupture in an uncomplicated pregnancy, without association with previous conditions, has been extremely rare [17, 18]. Up to 1943, there were 29 cases (the case of Vesalius included) of true spontaneous rupture of the liver (only two in pregnancy, Abercrombie in 1844 and Rademaker in 1943) [6].

11.1.3 Etiopathogenesis

11.1.3.1 Historical Perspective

One of the first mechanisms described, as in Rademaker's case, is rapidly rising blood pressure, with toxemia of pregnancy causing rupture of a blood vessel [6]. Devic and Beriel [2] and, later, Mazel have formulated this theory of the pathology of spontaneous rupture of the liver: *In traumatic rupture, the rupture is the cause of hemorrhage. In spontaneous rupture, the hemorrhage is the cause of the rupture. The chain of events leading to the rupture is infarct, hypervascularization at the periphery, rupture of a vessel, intrahepatic hemorrhage with resulting rupture of the tissue and production of a subcapsular hematoma which when rupturing the capsule permits the escape of blood into the peritoneum* [19].

11.1.3.2 Mechanism

In most cases, a liver rupture occurs in the third trimester of pregnancy or within the first 24 h postpartum. It occurs more often in the multiparous women above the age of 30 [10, 12, 20]. In 75% of the cases, it consists of a solitary injury of the right liver lobe (mainly the anterior and superior wall), in 11% of the left liver lobe, and a bilateral injury in 14% [21]. The pathogenesis of a spontaneous liver rupture as a complication of hypertensive disorders of pregnancy such as preeclampsia, eclampsia, or commonly HELLP syndrome remains unclear [11, 22, 23]. When hemorrhage follows delivery, one might suppose that the sudden decrease in intra-abdominal pressure or the stress of uterine contracture and the Valsalva maneuver or both may have encouraged the rupture.

Rademaker proposed the pathogenesis of spontaneous liver rupture through four stages [24]. A first *hepatic ischemic stage* is related to previously present preeclampsia or eclampsia giving rise to small zones of liver infarction. This is due to microvascular vasospasm, fibrin deposition in the hepatic sinusoids of eclamptic patients, and periportal necrosis. Obstruction of blood flow in the sinusoid may cause liver distention. This phase is followed by the second *phase of cicatrization*, tissue remodeling, and rising vascularization. Nevertheless, due to the poor tissue healing capacity associated with sustained intrahepatic hypertension and serious disorder of coagulation (in cases associated with HELLP syndrome when increased complement activation is also present [25]), multiple parenchymal microhemorrhages are induced, giving rise eventually to a *large hepatic hematoma* (third phase) [15, 26]. Finally, the persistent and growing hepatic hematoma causes *perforation of subcapsular hepatic hematoma* which further causes hypovolemic shock (fourth stage). However, there is no statistically significant correlation between the severity of the histologic findings of periportal hemorrhage and fibrin deposition and the clinical laboratory findings [27].

Hemolysis is the result of shearing of erythrocytes by fibrin strands that are deposited in the microcirculation, producing schistocytes. The syndrome also has been called microangiopathic hemolytic anemia. The histopathology of the liver in toxemia of pregnancy has been described consistently as showing fibrin plugs or strands in the sinusoids and hepatic arterioles with resultant areas of periportal necrosis [22, 28]. Vasospasm of the hepatic arterial circulation with resulting endothelial damage may lead to the platelet aggregation and fibrin deposition. Vascular disruption and occult parenchymal hemorrhage ensue. Coalescence of multiple focal areas of infarction and hemorrhage may progress to overt parenchymal hemorrhage and hematoma. A subcapsular hematoma, which can involve a large segment of the liver, ruptures with resultant intraperitoneal hemorrhage. In some cases, a hematoma may develop; however, the process may resolve, and the hepatic lesion may heal spontaneously without complete progression to the syndrome of spontaneous hepatic hematomas associated with pregnancy (SHHP).

Table 11.1 Underlying causes of spontaneous hepatic rupture during pregnancy

Bleeding from hemangioma/metastasis/hepatoma
Abdominal trauma
Infections (malaria, syphilis, amoebic abscess)
Hepatic tuberculosis
Hepatic sarcoidosis
Peliosis hepatis
Splanchnic artery aneurysms
Cocaine use
Anabolic steroid therapy
Systemic amyloidosis

The spectrum of pathology is highly variable. Evidence suggests that if an intraperitoneal rupture does not occur, the hepatic lesion may heal without a sequela. At the minimum, these patients with hepatic hematomas that have not ruptured mandate close observation in the peripartum period for signs of hepatic rupture and the syndrome of SHHP. Causes of spontaneous hepatic rupture during pregnancy are presented in Table 11.1.

11.1.4 Clinical Presentation

Patients with a spontaneous liver rupture present with right upper quadrant or epigastric pain (69.5%), hypovolemic shock (56%), nausea and vomiting (24.8%), and *Kehr's sign* (shoulder pain) (20.5%), and abdominal distention [14]. All preeclamptic patients with sudden-onset right upper quadrant pain had intraparenchymal or subcapsular hematomas [29].

On clinical examination, signs of peritonitis can be present, and fetal heart sounds are usually bad or absent. Hypovolemic shock within the first 24 h is mostly because of an excessive vaginal blood loss due to a failure of the uterus to contract after delivery of its contents. If the uterus is found to be contracted appropriately and no placental fragments are retained, a laceration of maternal soft tissues like a cervical or vaginal tear can be the cause of persistent vaginal blood loss. If all these gynecologic causes are excluded, intraperitoneal bleeding should be ruled out next.

Clinical presentation of HELLP syndrome is similar but not so dramatic. Patients complain of malaise (90%), epigastric or right upper quadrant pain (90%), or nausea or vomiting (50%), and some will have nonspecific viral syndrome-like symptoms [15].

11.1.5 Differential Diagnosis

Because a spontaneous hepatic rupture after a normal pregnancy is extremely rare, other more common causes for a postpartum acute abdomen and/or hypovolemic shock must be excluded. Cardiovascular instability without visible blood loss can also occur due to a traumatic laceration of the blood vessels resulting in a large vulvar, vaginal, or retroperitoneal hematoma. A large pulmonary embolism can also present with sudden cardiovascular instability without bleeding. It usually occurs after a deep venous thrombosis but can also occur primarily. The risk of embolism is tenfold higher after a CS than after a vaginal delivery. Another cause for a hypovolemic shock is a secondary postpartum hemorrhage. This is defined as vaginal blood loss occurring at least 24 h after the end of the third stage of labor and during the following 6 weeks. The spectrum of this condition can vary from inconvenient to fatal and occurs in almost 1% of the patients who delivered vaginally. Almost 50% of the patients have associated lower abdominal pain and uterine tenderness. The underlying cause is also an inability of the uterus to contract due to retained products of pregnancy and/or an intrauterine infection [30, 31].

11.1.6 Diagnosis

Because of the tendency to present with vague symptoms, the average delay in making the correct diagnosis of HELLP syndrome is 8 days [15]. The hemodynamic status of the patient determines the type of investigations.

11.1.6.1 Laboratory Findings

HELLP syndrome is diagnosed on the basis of laboratory findings. Several classification systems for women with HELLP syndrome have been developed, most of them based on platelet count. The *Mississippi 3-class classification* is

based on the lowest observed maternal platelet count: class 1 HELLP syndrome features severe thrombocytopenia with a platelet number ≤50,000/mL; class 2 HELLP syndrome features moderate thrombocytopenia with a platelet number 50,000–100,000/mL; and class 3 HELLP syndrome features mild thrombocytopenia with a platelet number 100,000–150,000/mL [16].

11.1.6.2 Transabdominal Ultrasound

Transabdominal ultrasound is a simple and reliable method of confirming the diagnosis of spontaneous hepatic hemorrhage [22]. The familiarity with and immediate availability of ultrasound to obstetricians make this the initial diagnostic procedure of choice in patients in whom the diagnosis is suspected either ante- or postpartum. If the patient is hemodynamically unstable, an urgent laparotomy must be performed. This can be preceded by an urgent ultrasound, if available.

11.1.6.3 Abdominal CT

In the hemodynamically stable patient, a CT scan with i.v. contrast is the most useful investigation. This allows the surgeon to quantify the liver injury, define the underlying hepatic disorders, and determine the treatment modalities (Figs. 11.1, 11.2 and 11.3). No correlation between the presence of abnormal liver imaging and the severity of hepatic function test abnormalities was found [32]. However, the severity of thrombocytopenia did correlate with the extent of hepatic imaging findings [32].

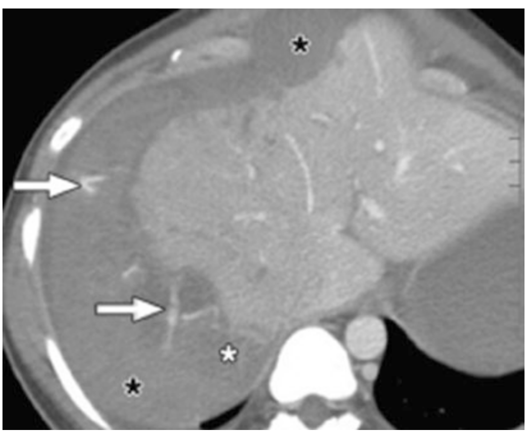

Fig. 11.1 Axial contrast-enhanced CT section shows non-enhancing hepatic foci (*white asterisk*) due to infarction and hematoma, foci of active bleeding (*white arrows*), and subcapsular and perihepatic hemorrhage (*black asterisks*) due to liver rupture from HELLP syndrome. Reproduced with permission from [33]

Fig. 11.2 Native CT scan shows a subcapsular hematoma with a peripheral hyperdense rim corresponding to a more acute bleeding. Note the sedimentation effect into the hematoma as an indicator for subacute bleeding. The capsule is intact. Reproduced with permission from [34]

11.1.7 Treatment

11.1.7.1 Historical Perspective

In 1943, Rademaker made a review of all published cases of spontaneous liver rupture in general and pregnant population defining important facts [6]:

- Careful observation by the family physician; otherwise, the patient would have died within a few hours.
- *Porro procedure* was the quickest means of removal of the fetus and the uterus to prevent any further bleeding from that source.
- The death of the fetus as a result of hemorrhage of the mother.
- Pleural effusion from the pressure of the pack on the diaphragm.
- Prompt multiple blood and plasma transfusions to save these desperately ill patients.

11.1.7.2 Medical Treatment

There is not a specific treatment of the evolving hepatocellular pathology that occurs in the

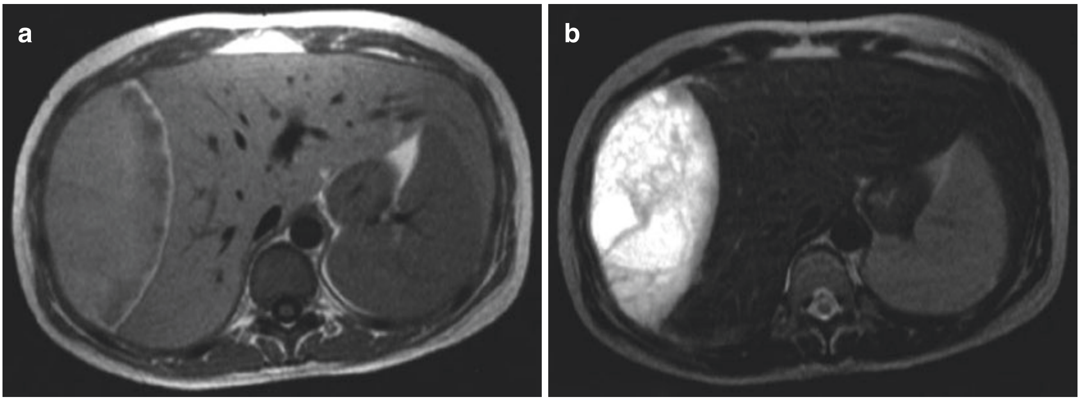

Fig. 11.3 Low-field (0.2-T) MRI shows a liquefied subcapsular liver hematoma with an isointense signal intensity at T2-weighted imaging (**a**) and an hyperintense appearance at the T1-weighted image (**b**). Typical intralesional changes of an older hematoma. Reproduced with permission from [34]

preeclampsia-eclampsia syndrome, and that may lead to spontaneous hepatic hemorrhage. Systemic anticoagulation is contraindicated. The underlying preeclampsia-eclampsia syndrome should be treated by the usual methods, such as administration of magnesium sulfate and the use of antihypertensive agents. When the hepatic lesion is suspected, hypertension should be controlled aggressively to prevent further progression and hemorrhage. Intraperitoneal rupture of the subcapsular hematoma is accompanied by hemorrhage and hypovolemia. Blood volume replacement is requisite, with an appropriate infusion of platelets and fresh frozen plasma. If the diagnosis is made antepartum, prompt termination of the pregnancy is mandatory, usually by emergent CS [35]. In the postpartum period, the chosen therapy mainly depends on the hemodynamic status and the severity of the liver injury. If the patient is hemodynamically stable and there is evidence of a contained subcapsular hematoma, a conservative treatment can be started. Patient must be admitted to the intensive care unit for close hemodynamic monitoring. Serial CT scans or ultrasounds must be performed in order to document expansion or rupture of the subcapsular hematoma. If the patient is hemodynamically unstable, two options are available: surgery or endovascular embolization of the hepatic arteries.

Successful nonoperative management of unruptured SHHP has been reported [22, 29, 36–38]. In some cases, 10 mg i.v. of dexamethasone every 12 h has been administered, aiming to improve platelet recovery and to shorten the evolution time of HELLP syndrome.

11.1.7.3 Percutaneous Techniques

Occlusion of the hepatic artery has been reported for treatment of hemorrhage due to a variety of conditions, including hepatic trauma, ruptured hepatoma, and spontaneous hepatic hemorrhage. The technique of percutaneous angiographic embolization allows for the most precise localization of the site of hemorrhage and is highly successful in arresting hemorrhage (Fig. 11.4). The method applied depends mostly upon the severity of the shock and the availability of an experienced interventional radiologist. The major advantage of embolization is its less invasiveness. Hepatic artery interruption has been well tolerated in the general population [39]. The right and left hepatic arteries, or both, can be occluded selectively. Transient elevations in the aspartate transferase and alanine transferase levels will result. In a liver with significant acute or chronic disease, the degree of hepatic dysfunction that follows hepatic artery occlusion may be accentuated. If the occlusion is proximal to the origin of the cystic artery, acute gangrenous cholecystitis may occur. Areas of focal hepatic necrosis can

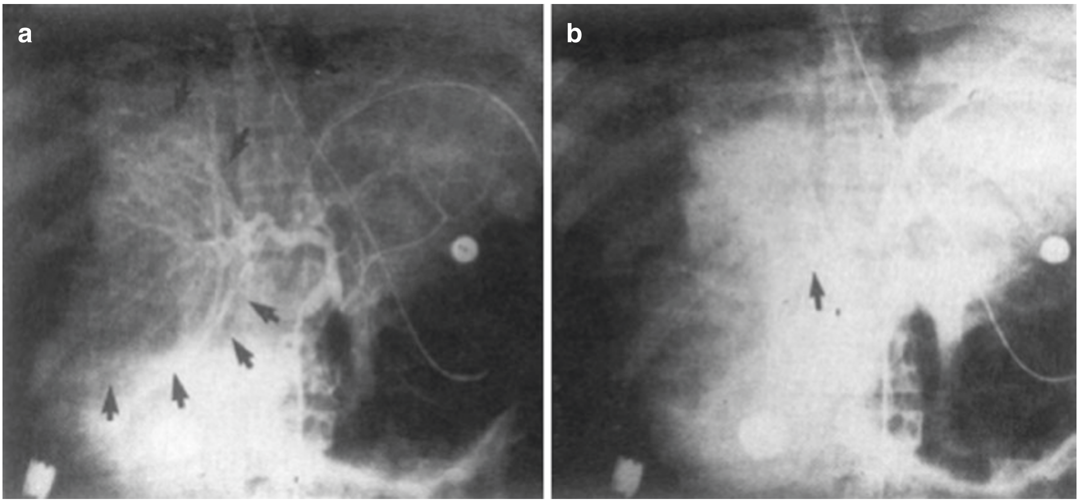

Fig. 11.4 (**a**) Hepatic arteriogram of a patient with bleeding subcapsular hematoma. *Arrows* identify multiple pseudoaneurysms with bleeding. (**b**) Arteriogram after embolization of right hepatic artery (*arrow*). Reproduced with permission from [40]

develop with or without secondary infection. Hypotension should be avoided after hepatic artery occlusion to maximize hepatic arterial flow. Supplemental oxygen may be administered. Hepatic perfusion through arterial collaterals may develop as little as 10 h after hepatic artery occlusion [39].

11.1.7.4 Surgical Treatment

Indications for surgery are [41]:

- **Evidence of hemodynamic instability**
- Continued blood loss
- Increasing pain
- Expansion of the hematoma
- Infection of the hematoma

Several surgical modalities have been described, depending on the severity of the rupture which can be estimated on diagnostic imaging modalities or intraoperatively (Fig. 11.5).

Intraoperative Hepatic Artery Occlusion

Some prefer intraoperative hepatic artery occlusion as the primary therapy of SHHP rather than tamponade of the hepatic hemorrhage with abdominal gauze packing [40].

Liver Packing

The bleeding should be controlled with liver packing first. Local measures such as topical hemostatic agents and suture ligation of surface bleeders are of limited value, especially when dealing with hemorrhage from large areas of denuded and friable liver in patients with associated clotting deficiencies. Then CS is made to save the baby and enable more space for definitive liver surgery if indicated.

Abdominal packing for spontaneous hepatic rupture associated with pregnancy in the period 1976–1990 showed an 82% survival rate [13]. The recommendation was that abdominal packing should be the primary treatment for ruptured hepatic hematoma [42]. An analysis of the references cited by Smith et al. [13] reveals that in at least six of the reports, significant numbers of the patients were not treated with perihepatic packing, but with local measures, including oxidized cellulose or gelfoams [11, 28, 43–45]. It is unclear if these patients exhibited the full spectrum of the syndrome, including rupture of the hepatic hematoma with life-threatening hemorrhage, or had contained nonbleeding hematomas.

Packing should be reserved for patients in whom the diagnosis of SHHP is made at the time of CS and in whom a Pringle maneuver incompletely

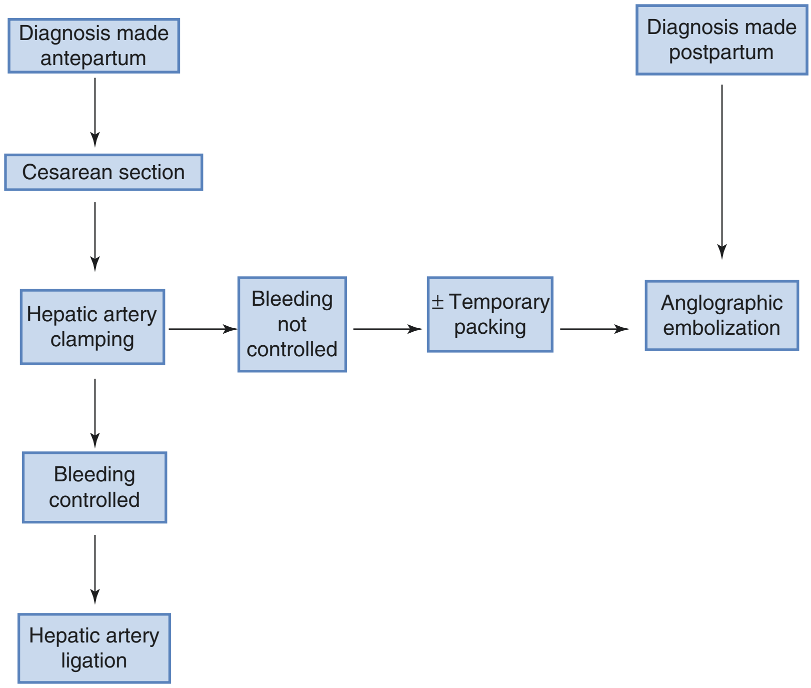

Fig. 11.5 Algorithm for the treatment of *spontaneous* hepatic rupture in pregnancy (see text for details). Reproduced with permission from [40]

controls the hepatic hemorrhage. In this situation, hepatic packing may have a role as a temporizing measure en route to the angiography suite. It does require a second operative procedure for removal of the packs, and sometimes repeated laparotomies with packing are needed. However, if in the operating room, the bleeding is controlled by clamping of the right, left, or common hepatic artery, hepatic arterial ligation is preferable as a definitive treatment.

Argon Beam Coagulation

Argon beam electrocoagulation can be used alone or before packing to lessen the intensity of the bleeding. The hematoma is unroofed and hemostasis obtained using the argon beam coagulator [46]. The argon beam coagulator delivers a high-frequency alternating current directly to the tissue, using ionized argon gas as a medium [47]. Argon gas is used because it is inert and nonflammable. The energy delivered (40–150 W) is only slightly higher than standard monopolar electrocautery (10–120 W) [47]. Heat is evenly applied to bleeding vessels and surrounding tissue, thus obtaining hemostasis without tissue contact and effectively sealing the wound. It differs from conventional spray electrocautery which requires direct contact to distribute electrical energy. This is often unevenly applied and contributes to tissue necrosis. The reduced depth of tissue penetration needed with the argon beam coagulation results in minimal tissue damage. Another shortcoming of conventional electrocautery is its relative ineffectiveness in a bloody field. The argon beam coagulator is particularly useful in situations of significant hemorrhage because of its ability to displace pooled blood and apply the needed energy to the underlying tissue, thus halting the source of bleeding. The eschar that also forms after argon beam coagulation is reportedly more adherent and is associated with less late rebleeding than conventional hemostatic methods [47].

Segmental Liver Resection

Major liver resections should be avoided if possible because of the friable consistency of the liver [9]. Also, thrombocytopenia and coagulopathy are almost always present, making any invasive procedure potentially treacherous.

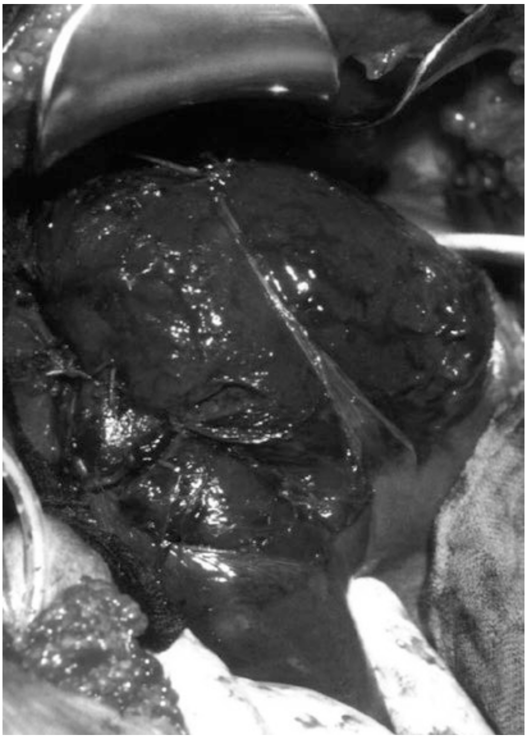

Fig. 11.6 The explanted liver showed massive tears in both lobes with a maximal depth of 7 cm. Unsuccessful liver packing was attempted twice. Reproduced with permission from [34]

Liver Transplantation

There are three principal indications for liver transplantation which is the last surgical option (Fig. 11.6) [34, 48, 49]:

- **Hemorrhage cannot be contained after (repeated) liver packing**
- Acute liver failure (hepatorenal syndrome?)
- Massive destruction of both liver lobes

11.1.7.5 Obstetric Management

If a rupture occurs during pregnancy, delivery of the fetus is one of the first steps. A classical Pfannenstiel incision is, however, not suitable because the full abdomen cannot be visualized unless a second upper abdominal incision is made. A median laparotomy is, therefore, the recommended approach because it has the great advantage of visualizing the entire abdomen, the speed of execution, and less blood loss [31].

11.1.8 Prognosis

Up to 1943, there were 29 cases (the case of Vesalius included) of true spontaneous rupture of the liver, and only two of these complicated pregnancy (Abercrombie 1844, the patient died after normal vaginal delivery, and Rademaker in 1943 controlled the hemorrhage by packing, and after a stormy convalescence, the patient recovered but the fetus died) [6].

11.1.8.1 Maternal Outcome

Up to 1976, the rate of maternal mortality during liver rupture was 59% [10, 50, 51]. Two decades later, maternal mortality was lowered to 15–25% [13, 52, 53]. In the collected reports of 15 patients treated with hepatic artery ligation/occlusion (radiologically or surgically), the mortality was 29–37% [40, 43, 54–58].

11.1.8.2 Fetal Outcome

Up to 1976, the rate of fetal mortality during liver rupture was 62% [10, 50, 51]. Two decades later, fetal mortality was lowered to 42% [53] and recently to 25% [52]. If the fetus survived, important hypoxic-ischemic encephalopathy has been reported in a significant number of cases.

11.2 Peptic Ulcer Bleeding

11.2.1 Introduction

Pregnancy seems to have a beneficial effect on peptic ulcer (see Chap. 4). Clark in 1953 investigated dyspeptic symptoms during 313 pregnancies in 118 women with the diagnosis of peptic ulcer before pregnancy [59]. There was a remission of ulcer symptoms in 88% of the pregnancies. More than 50% of these women claimed to have been completely symptom-free during the whole pregnancy; the remainder had minor symptoms which they regarded as unconnected with the ulcer. In the remaining 12%, symptoms persisted which were indistinguishable from those of ulcer, and 14 women were admitted to hospital for treatment of the "indigestion." In no

case did hemorrhage or perforation occur during the pregnancy.

The first known case is an autopsy report by LePlay in 1905 showing hemorrhage from PUD in the seventh month of pregnancy [60].

11.2.2 Incidence

Small hemorrhages from the upper part of the alimentary tract do not appear to be very rare in pregnancy, although Avery Jones in 1947, investigating for ulcer activity a series of 10,000 women attending an antenatal clinic, found only one case of mild hematemesis, and no ulcer could be demonstrated [61]. In a series of 587 cases of hematemesis and melena admitted at Whittington Hospital during the 4-year period 1957–1960, there were four pregnant women (MacCaig JN, 1962, personal communication). These data show that only 0.7% of bleeding peptic ulcers occur during pregnancy. It may be that the small number of proven cases is due to a reluctance to carry out radiological investigations during pregnancy before the era of endoscopy. If investigations were done after the birth of the child, the ulcer would probably have healed. Up to 1971, 31 perforations and 32 cases of hemorrhage from proved peptic ulcer during pregnancy have been reported [62]. The ratio of gastric and duodenal ulcers in pregnancy and also bleeding peptic ulcers during pregnancy is not known. Peptic ulcer bleeding occurs in the late third trimester or during the first days postpartum [63]. There are only several case reports of operated bleeding peptic ulcers (Table 11.2).

Table 11.2 Hemorrhage from peptic ulcers during pregnancy (1905–1998)

Authors	Week of pregnancy	Lesion/procedure	Maternal outcome	Fetal outcome
Le play, 1905 [60]	7th month	Gastric ulcer	Died	Abortion
Mulsow and Brown, 1936	35	Duodenal ulcer	Died	Live (twins)
MacNalty, 1937 [70]	Puerperium	Gastric ulcer	Died	Not recorded
Le Winn, 1947	37	Duodenal ulcer/conservative	Live	Died
Bernstine, 1948 [64]	7th month	–	Live	Live
	4th month	–	Live	Stillborn (5th month)
	7th month	–	Live	Stillborn (8th month)
Johnston, 1953 [66]	Labor	Duodenal	Died	Died
Durst and Klieger, 1955 [73]	Term	Gastric	Died	Live
Vasicka, 1957 [67]	20	Duodenal/castrectomy	Live	Died/C-section, 33 weeks
Crisp, 1960		?		C-section
Stevenson, 1962 [74]	Term	Gastric/castrectomy	Live	Died at C-section
Strange, 1962 [69]	28	Duodenal	Live	Live
Möbius, 1962 [75]	8th month	Duodenal/exploration, CS	Died	Died
Wendt, 1965 [76]	36	Gastric/gastrectomy	Live	Live/vaginal, 36 weeks
Tietz, 1966 [77]	2nd–3rd month	Gastric/conservative	Live	Live/vaginal, term
Diltz Jr., 1967 [78]				
King, 1967	7th month	Duodenal/sutures, vagotomy	Live	Live/vaginal, term
Jones, 1969 [79]	38	Gastric/gastrectomy	Live	Live/C-section
Becker-Andersen, 1971 [62]	35	Gastric/gastrectomy	Live	Live/CS
	38	Duodenal/		Died/vaginal
Ioan, 1973 [80]	Puerperium			C-section
Funcken, 1977 [81]	Labor	Duodenal/sutures	Live	Live
Beyne-Selmi, 1978 [82]	Term	Gastric/conservative	Live	Died/vaginal
Aston, 1991 [83]	Puerperium	Duodenal/vagotomy, pyloroplasty	Live	Live
Palade, 1998	37	Duodenal/sutures	Live	Live/C-section

11.2.3 Risk Factors

In 1948, Bernstine and Friedman reported four cases of hemorrhage from peptic ulcer in pregnant women [64]. All of these women had been treated with *progesterone* for threatened abortion before the onset of the peptic ulcer hemorrhage.

11.2.4 Diagnosis

A bleeding peptic ulcer is diagnosed by esophagogastroduodenoscopy (EGD). Before the era of endoscopy, peptic ulcers were diagnosed with the radiological examination. Due to the ionizing radiation, it was contraindicated during pregnancy. Therefore, for many cases of peptic ulcer hemorrhage during pregnancy in the first half of the twentieth century, the diagnosis was never confirmed [65].

11.2.5 Treatment

11.2.5.1 Medical Treatment

Today, with potent acid suppression medications, most of peptic ulcer bleeding can be treated without operation. During the long period of occurrence during pregnancy, most of these bleedings stopped with medical management [63]. If needed, EGD intervention is performed. Endoscopic interventions are not contraindicated during pregnancy (see Chap. 2). Johnston, in a period between 1939 and 1953, found two with duodenal ulcer, one complicated by hemorrhage and one by perforation [66]. Bleeding ulcer responded to conservative management.

11.2.5.2 Surgical Treatment

In the general population, the type and location of the bleeding peptic ulcer dictate the type of surgical procedure. Due to only several cases operated during pregnancy, these surgical principles should be applied in pregnant patients. In 1957, Vasicka reported a case of massive gastrointestinal hemorrhage from peptic ulcer. The first reported gastric resection with gastroduodenostomy was performed by Vasicka in 1957 in the 20th week of gestation. Hypertension, albuminuria, and vaginal hemorrhage developed in the 28th week, and a viable infant was delivered by CS during the 33rd week [67]. The first partial gastrectomy for a perforated duodenal ulcer in pregnancy is described by Burkitt in 1961 (see Chap. 4).

There are three known cases of surgical treatment for hemorrhage from duodenal ulcer occurring during pregnancy. In one case, vagotomy and pyloroplasty were performed [68], and in another two cases, partial gastrectomy was made [62].

11.2.6 Prognosis

11.2.6.1 Maternal Outcome

Maternal mortality from 1905 to 1955 was 83% and from 1905 to 1962 lowered to 71% [69]. After 1965, the mortality dropped to almost 0% (Table 11.2).

Due to the extreme rarity of the disease, maternal mortality, in studies during the first half of the twentieth century, was also evaluated in cumulative pregnancy or puerperal deaths. MacNalty found only one death from hemorrhage due to a gastric ulcer in 770 puerperal deaths in 1937 [70]. Hooker studied 350,000 pregnancies over a 3-year period (1930–1932) and found only one death from perforation of a gastric ulcer [71]. Sandweiss found one death due to a perforated duodenal ulcer in 70,310 pregnancies during a 10-year period (1928–1937) in various Detroit hospitals [72]. In 1943, Sandweiss, in a review of the literature on deaths due to perforation and hemorrhage from gastroduodenal ulcer during pregnancy and puerperium, found only 14 cases. In seven cases, they were gastric ulcers and in seven, duodenal. All of the 14 patients died postpartum, and premature delivery occurred in four [72]. Carangelo reported four cases of massive gastrointestinal hemorrhage in pregnancy, with three deaths [65]. Three of the four patients had an eclamptic syndrome with hypertension, edema, convulsions, oliguria, and albuminuria, and all four had a septic course with fever. The onset of labor in three of the patients occurred 24–48 h after the onset of hematemesis. There were three stillbirths and one premature but viable infant. Reports of only

seven cases of hemorrhage from proved ulcers could be found in the literature (Table 11.2).

11.2.6.2 Fetal Outcome

Fetal mortality from 1905 to 1955 was 60% and from 1905 to 1962, 67%, respectively (one case did not report fetal outcome) [69]. After 1965, fetal mortality dropped to less than 30% (Table 11.2).

11.3 Mesenteric Ischemia

11.3.1 Mesenteric Vein Thrombosis

> *… not everyone is aware that violent abdominal pain, ileus, and collapse may mean mesenteric vascular occlusion ….*
>
> Warren and Eberhard, 1935.

11.3.1.1 Historical Perspective

Mesenteric vein thrombosis (MVT) was first summarized as a cause of intestinal infarction in 1895 by Elliot, who treated the infarcted bowel with resection, creating two stomas and reanastomosing those 2 weeks later. Charles Hilton Fagge (Fig. 11.7), at Guy's Hospital, London, published the first case in puerperium in 1876 [84]. A woman died a month after delivery in a few hours after the onset of severe abdominal symptoms. An autopsy showed thrombi in the superior mesenteric veins extending into the trunk of the portal vein nearly to the point where it breaks up into its branches. The thrombosis extended into the veins beyond the territory that was congested. There was no endocarditis or any evidence of peritonitis or any cause for internal strangulation found.

11.3.1.2 Incidence

MVT is an extremely rare condition in the general population and accounts for 0.002–0.06% of all inpatient admissions [86], 0.01% of all emergency surgical admissions, and <1/1000 laparotomies for acute abdomen [87]. The venous collateral circulation of the inferior mesenteric vein is more elaborate than that of the superior; therefore, MVT of the inferior mesenteric vein followed by infarction of the descending colon, it is exceedingly rare. The literature review of 372 cases of MVT in the general population (1911–1984) found that the condition was most common in the sixth and seventh decades of life [88], while recent series found the most common occurrence between 45 and 65 years [89, 90]. In autopsy studies, MVT is found in 0.2–2% of the general population [86] and in less than 1% of patients with mesenteric ischemia [86]. In pregnancy and puerperium, up to 1963, there were 15 cases described [91–94]. Of these, 27% (4/15) followed abortions, 13% (2/15) occurred during pregnancy, and 53% (8/15) during puerperium. One case was not confirmed. After 1963, a similar number of patients was published [95–99].

Fig. 11.7 Charles Hilton Fagge (Hythe, Kent, England 1838–1883) (Courtesy of the Gordon Museum, King's College London). His maternal uncle, John Hilton (1804–1878), was an anatomist and surgeon, President of the *Royal College of Surgeons*, and surgeon extraordinary to Queen Victoria. His father, Charles Fagge, and his grandfather were also physicians. Reproduced with permission from [85]

11.3.1.3 Risk Factors

Three factors, usually referred to as Virchow's triad, are concerned in the formation of every thrombus. These are damage to the vascular endothelium, changes in the velocity and character of the local bloodstream, and changes in the constituents of the blood. MVT is a very uncommon surgical pathology frequently associated with known coagulation defects [96–98]. The maternal risk of thromboembolic episodes is increased eight times in the presence of any one of the coagulopathies [100]. The incidence of the factor V Leiden mutation may be as high as 46% in patients with a history of venous thromboembolism during pregnancy [101].

The presence of MVT is found also when there is no detectable coagulation error and is extremely rarely encountered in pregnancy [96, 102, 103]. This condition is attributed to physiological hypercoagulability which occurs during pregnancy due to multiple factors including a rise in factors VII and VIII and fibrinogen and reduction in fibrinolytic activity [102]. But a rise in platelet count together with an increase in platelet stickiness maximal on the 12th day of puerperium has been demonstrated [104]. There are only four cases of *primary* (*idiopathic*) *MVT* with no precipitating factor found for the development of MVT [96, 102, 105, 106].

A specific group of MVT has been reported in pregnancy in association with certain surgical and medical comorbidities which include repeated abdominal surgery, CS, appendectomy for gangrenous appendicitis, elective laparoscopic cholecystectomy, mesenteric cyst excision, vesicoureteral reflux, and mistaken intake of oral contraceptives during pregnancy (Table 11.3). The issue with the association of risk factors and MVT is that patients sometimes have additional risk factors like heavy smoking [107] or high BMI. The anatomic location of venous thromboembolism associated with IVF cycles has been suggested to differ from those seen in the general population. In venous thrombosis associated with IVF, the veins of the upper extremities and neck are involved in 80% of reported cases, whereas only 11% of deep vein thrombosis diagnosed in the general population involves the upper extremities [108]. Further, 97% of upper extremity deep vein thrombosis reported during pregnancy was associated with assisted reproductive technology [109].

Table 11.3 Primary and secondary MVT risk factors in pregnancy and puerperium [95–99, 102, 105–107, 110, 111]

Hypercoagulopathies
Oral pills during pregnancy or puerperium
Postoperative
Single or repeated abdominal surgery
Cesarean section
Cytomegalovirus infection (with complications)
Chronic idiopathic MVT
IVF pregnancy
Hemoglobinopathy
Primary (idiopathic)
Smoking
Obesity
β-thalassemia
Antiphospholipid syndrome
Abnormal fibrinogen
Homocystinuria
Paroxysmal nocturnal hemoglobinuria
Thrombocythemia
Abdominal trauma
Abdominal sepsis
Myeloproliferative disorders
Cancer

11.3.1.4 Clinical Presentation

Clinical symptoms of *acute* MVT are variable, nonspecific, and difficult to differentiate from arterial occlusion. In most cases of acute MVT, the main symptom is abdominal pain lasting from several days to more than 3 months [92], first cramp-like before becoming continuous when peritonitis supervenes. They continued to have bowel movements initially, becoming constipated later. Patients had pain out of proportion to abdominal tenderness, an important differential point in diagnosis [112]. Other symptoms are nausea/vomiting, fever, and abdominal distention. The tendency toward hemoconcentration is also characteristic and probably reflects the slow progress of the disease, allowing sequestration of extracellular fluid in the gut. The occult blood is commonly found in the stools [113]. On rectal examination, there may be blood on the

examining finger. If hematemesis in acute form is found, then splenic vein thrombosis is present. Splenic vein thrombosis is not necessarily followed by hematemesis.

Subacute or *chronic* MVT is usually asymptomatic due to the development of collateral vessels, but when it is combined with portal vein thrombosis, esophageal variceal bleeding with hematemesis may occur [90]. Most patients in the general population using oral contraception had at least 2 weeks of symptoms such as abdominal pain, discomfort, anorexia, vomiting, and change in bowel habits [114]. Sometimes, the leading presentation can be spontaneous abortion or stillbirth [92].

11.3.1.5 Diagnosis

Clinical diagnosis of MVT is usually difficult, and it is frequently delayed due to lack of awareness among primary physicians and absence of active signs in early stages of the disease. Furthermore, the early features of the disease get masked by the effects of pregnancy. Early diagnosis is possible only if a high degree of suspicion is exercised in cases of severe abdominal pain with the absence of positive physical signs.

Almost all patients present with leukocytosis with elevated hematocrit, but these are not helpful for diagnosis [115]. There is an 80% incidence of elevated white cell count in cases of MVT in the general population [116]. The diagnosis can be confirmed with color Doppler ultrasound [117] which is widely available, cheaper, feasible for emergency imaging, and applicable in pregnancy due to lack of need for X-rays or potentially harmful intravenous contrast, but this modality has been shown to have only 70% sensitivity in general population [89].

Contrast-enhanced abdominal CT in the general population currently holds a sensitivity of >90% and is the diagnostic method of choice (Fig. 11.8). Magnetic resonance imaging offers no distinctive advantage over CT [90]. Some authors claim that angiography findings in the general population of veno-occlusive disease are less sensitive. The angiography showed only 55% sensitivity and has not been suggested as a primary diagnostic modality [90].

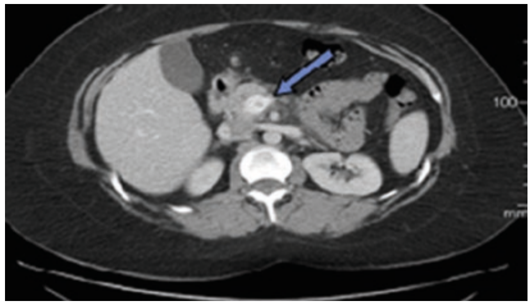

Fig. 11.8 Abdominal CT scan with superior mesenteric vein thrombosis (*blue arrow*) in a patient on an IVF program. Reproduced with permission from [110]

Often, definitive diagnosis is made during surgical exploration mostly due to the acute abdomen. If there is no strangulation, volvulus, mesenteric thromboembolism, or cocaine abuse should be excluded [118].

11.3.1.6 Treatment

Management involves multiple disciplines including surgery, clinical hematology, obstetrics, and neonatology and depending on the presentation of a particular case. Most importantly, the treatment depends on the stage of the disease [90].

Surgery

Explorative laparotomy is indicated for patients with symptoms and signs of acute abdomen or suspected or confirmed intestinal infarction (Fig. 11.9) by diagnostic modalities. Consideration should be given to the use of intra-arterial papaverine to reverse (arterial) spasm and cause relaxation of the uterus, preventing spontaneous abortion or preterm labor. The thrombolytic agents via operatively placed catheters, together with continued heparin, may prevent extension of infarction (see further paragraphs for pregnant population).

If there are segmental gangrenous segments, minimal resections should be performed to minimize the possibility of short bowel syndrome. Multiple resections with anastomoses with or without proximal stoma are recommended. Another option after multiple segmental resections is to close (potentially) viable bowel segments by stapling and abdomen left open with

Fig. 11.9 Segmental gangrene of the small intestine without any obstruction and perforation due to mesenteric vein thrombosis. Reproduced from [105] under the CC Attribution License

vacuum-assisted closure (VAC) with 125 mmHg continuous negative pressure (see Chap. 22) in the aim of assessing the viability of remaining bowel after 24 and 48 h [99]. At the second and third surgical looks, some intestinal segments could require subsequent additional resections. Eventually, after 48 h of open abdomen management, the intestinal continuity should be restored. The abdominal wall should be primarily closed without aponeurotic defect. The rare cases of laparostomy use in pregnant women are discussed in detail in Chaps. 3 and 22.

As the enlargement of the spleen in protein C deficiency and its gastric pressure could become prominent together with anemia and leucopenia in addition to mild-severe thrombocytopenia, splenectomy seems to be an appropriate choice together with the periodic use of protein C concentrate [119].

Thrombectomy

Other treatments such as peripheral or regional thrombolysis with or without surgical thrombectomy and a combination of surgical thrombectomy and regional heparinization have been reported in the general population. There are anecdotal reports of venous thrombectomy in the general population, but this has not shown improved outcome and is generally not recommended. In pregnancy, treatment with thrombolytics is not advocated [102].

Anticoagulation

In the patients without bowel infarction or peritonitis, anticoagulation with heparin followed by warfarin after delivery is the mainstream therapy [90]. Heparin has been shown to prevent recurrence of thrombosis after intestinal resection (14% vs. 26% [88]) and to be associated with lower mortality when recurrence does occur (22% vs. 59% [88]). In anticoagulated patients not undergoing surgery, most thrombosed veins will partially or completely recanalize over time. During pregnancy, LMWH is recommended in order to avoid the possible side effects of warfarin on the fetus, especially its teratogenic and bleeding effects. There are no guidelines for the duration of anticoagulation after pregnancy, and decisions on a case-by-case basis need to be taken by expert clinical hematologists [102]. In patients with inherited hypercoagulable disorders (i.e., protein S, protein C, antithrombin III deficiencies, and factor V Leiden mutation), lifelong anticoagulation is warranted. For a general population with reversible predisposing causes, at least 6 months of anticoagulation is recommended [120].

Guidelines for anticoagulation management strategies for various clinical situations before and after controlled ovarian stimulation are published [121, 122]. Patients with a history of prior MVT should be placed in the clinical classification of “previous episode(s) of venous thromboembolism receiving long-term anticoagulation.” It is recommended switching from oral anticoagulants to LMWH therapy (e.g., enoxaparin 1 mg/kg every 12 h) before controlled ovarian stimulation and continuing this regimen throughout pregnancy [121, 122]. The recommendation is refraining from the administration of LMWH for 24 h before egg retrieval and restarting therapeutic anticoagulation 3 h after egg retrieval [121, 122]. In the setting of IVF, associated MVT, and the absence of large studies, lifelong oral anticoagulation in patients at low risk for bleeding and full anticoagulation with LMWH per the above protocol during repeat IVF cycles is considered prudent. However, controversy in management for the prevention of venous thrombosis still exists after delivery. Though the

induction of oral anticoagulation in protein C deficiency has been widely used, it carries significant risks in a patient with esophageal varices and thrombocytopenia [119].

Obstetric Management

Continuation of Pregnancy

The decision on continuation [96, 102] or termination [105] of pregnancy is taken as per the case and available facilities. Even in cases with several operations due to gangrenous bowel and open abdomen, the pregnancy can be uneventfully carried to full-term vaginal delivery [99]. Prevention and treatment of preterm labor are presented in Chap. 23.

Mode of Delivery

If the pregnant woman has proven PVT, every effort should be made to prevent further complications during and after delivery. The straining and bearing down that takes place during vaginal delivery have also been reported to result in a marked but transient portal vein pressure in all pregnant women. Thus, the avoidance of vaginal delivery and the use of CS should minimize the portal vein pressure increase and reduce the possibility of variceal bleeding [119, 123].

11.3.1.7 Prognosis

The prognosis of MVT does not appear as ominous as that associated with arterial thrombosis in the general population [90], with the mortality in general population in the range of 13–50%. The subgroup with oral contraception as the cause had high rates of the mortality and morbidity in the review from 1977 to 50% of the patients died and 50% required at least two operations. Arterial thrombosis carried twice the mortality of venous thrombosis but was half as common [108]. In pregnancy, up to 1963, out of 15 described cases mortality was 87% (13/15), and the two patients that survived were from the last year (1963) of the analyzed period [91, 92].

11.3.2 Portal Vein Thrombosis

11.3.2.1 Introduction

Portal vein thrombosis (PVT) shares the same or similar characteristics as MVT inclusion localization, risk factors, diagnosis, and therapy.

11.3.2.2 Incidence

PVT is even rarer in pregnancy than MVT with only a few cases published [119, 124–126]. The cases were equally distributed through trimesters: one in the first [125], two in the second [124, 126], and one in the third trimester [119].

11.3.2.3 Risk Factors

Risk factors are the same as for MVT (Table 11.3) which are the same as for MVT during pregnancy. The concurrence of several disorders seems to be relatively common in PVT in adults, and extensive investigation should be considered in these patients. Probably the only risk factor more influential on the development of PVT than MVT is cirrhosis, but due to the extremely low incidence of both conditions in this age group, conclusions cannot be made.

11.3.2.4 Clinical Presentation

Clinical presentation is different from MVT. Most patients present with a short history of acute right hypochondrial pain that lasts from hours to several days and fever of around 38 °C [125]. The signs include tachycardia, fever, and tenderness in the upper right abdominal quadrant without peritoneal irritation.

11.3.2.5 Diagnosis

Transabdominal Ultrasound/Doppler

Diagnosis is made by ultrasound, or more specifically by Doppler. Unlike contrast CT and helical CT associated with CT angiography, color Doppler does not involve the potentially harmful intravenous injection of contrast. Also, unlike MRI and 3D magnetic resonance portography with contrast, color Doppler is more widely available, cheaper, and feasible on an emergency basis.

Urgent abdominal ultrasound is sometimes performed to rule out acute cholecystitis but can demonstrate well-defined homogenous hyperechoic oval-shaped formation in the splenomesenteric confluence and/or branches of the portal vein. Color Doppler study confirms these findings by showing margination of the colored flow in the residual lumen. Splenic and mesenteric veins should be visualized because their thrombosis could lead to bowel ischemia. The hepatic artery shows increased compensatory flow. Collateral venous circulation should be verified or excluded because it helps to establish a definitive diagnosis. The color Doppler sonographic features of acute thrombosis in the portal vein or superior mesenteric vein are as follows:

1. The thrombosed vein usually displays an echogenic appearance (70% of the cases in the general population) [127]. Ultrasound study shows a dilated vein with the loss of respiratory motions and venous distention upstream of the thrombosis. Transient ascites may be seen, denoting an acute portal hypertension. Color Doppler confirms the diagnosis by demonstrating either the absence of intraluminal colored flow in case of complete thrombosis or eccentric or marginated colored flow in case of partial thrombosis. Also, Doppler study demonstrates an increased compensatory flow in the hepatic artery as well as periportal collateral venous circulation that may develop after 1 week [127].
2. Alternatively, the thrombosed vein displays an anechoic appearance (20–30%). Ultrasound may miss the thrombus, and color Doppler constitutes the modality of choice as it enables demonstration of the colored filling defect within the venous lumen [127]. When PVT is confirmed by Doppler, complete coagulation profile should be obtained.

11.3.2.6 Treatment

Anticoagulation

Prompt treatment of PVT is essential in order to prevent extension to the superior mesenteric vein, splenic vein, and hepatic vein which could lead to the development of hepatic or mesenteric infarction. Prompt treatment could also prevent progression to portal hypertension with the risk of variceal hemorrhage [119]. Furthermore, early treatment could result in complete lysis of the clot, and the resolution of the clot could be as early as 4 days but could take up to 1 month.

Interventional Techniques

The use of fibrinolytic infusion by the systemic route, transhepatically, or via the superior mesenteric artery have shown controversial results in general population [128]. Percutaneous interventional techniques such as balloon dilatation and stenting have been effective in some cases with acute, recent PVT; however, these treatment modalities do not prevent rethrombosis [128]. Therefore, patients at risk should be kept on prophylactic anticoagulants for life in order to prevent rethrombosis.

Response to Therapy

Response to therapy in pregnant patients cannot be estimated due to the extremely small number of patients, but color Doppler provided reliable means of monitoring response to therapy of the PVT [127].

11.4 Inferior Epigastric Artery Bleeding

11.4.1 Anatomy

The inferior epigastric artery (IEA) arises from the external iliac artery deep to the inguinal ligament. It both serves as a surgical landmark and constitutes a potential target for injury during inguinal hernia repair. The IEA divides deep to the rectus sheath into two branches: an ascending branch that anastomoses at the umbilicus, medial to the rectus sheath, with the abdominal branch (or superior epigastric artery) of the internal thoracic artery, and a descending branch that gives off obturator branches that course along the

ischium and anastomose with the obturator artery and pubic branches, which in turn course along the pubic rami and reach the pubic symphysis.

11.4.2 Historical Perspective

Rectus sheath hematoma (RSH) is an ancient disorder first accurately described by Hippocrates and mentioned by Galen. In 1925, Carey Culbertson reported two cases with consideration of its gynecological and obstetrical significance [129]. Thomas Stephen Cullen (Fig. 11.10), in 1918, was first to describe bluish periumbilical discoloration due to ruptured ectopic pregnancy and then with Brödel in 1937, at Johns Hopkins Hospital, reported two cases of spontaneous hematoma of the rectus abdominis during pregnancy [130, 131]. Both were black patients. The resolution was uneventful in one with a 7-month pregnancy, but operative exploration was carried out on the other with success.

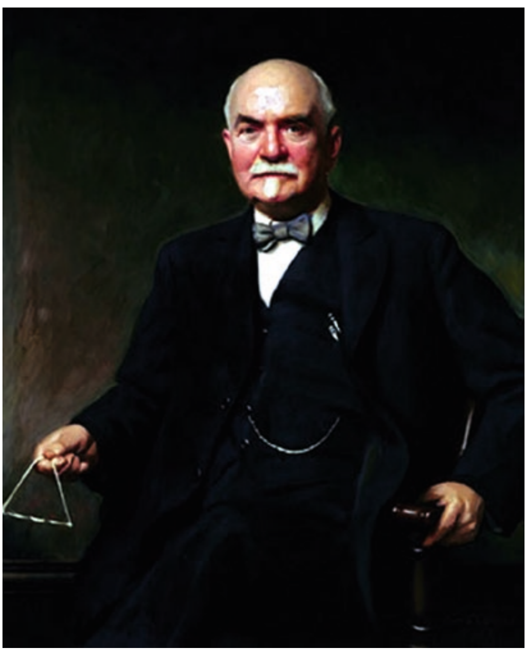

Fig. 11.10 Thomas Stephen Cullen (1868–1953); painting by Thomas C. Corner; oil on canvas, 48 by 40 in., 1907 (Courtesy of the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions). Reproduced with permission

11.4.3 Incidence

11.4.3.1 Spontaneous Rectus Sheath Hematoma

Maxwell in 1929 found 11 cases [132]. Of these, 73% (8/11) were during pregnancy and 27% (3/11) during labor. Torpin in 1943 analyzed 27 reported cases in pregnancy [133]. In the general population, 60% are on the right side and more than 80% in the lower quadrants [134]. Riera et al. in 2009 collected 52 cases during pregnancy [135]. The incidence of spontaneous IEA bleeding is lower due to several reasons:

- More cautious pregnant women less exposed to blunt or penetrating abdominal/pelvic trauma (more at home, less car driving)
- Avoidance of heavy lifting
- Avoidance of closed spaces and people with infectious diseases mostly respiratory conditions
- Lower incidence of surgical or other invasive interventions during surgery

11.4.3.2 Post-cesarean Section

Early reoperation rate after CS in India is 0.45–0.6% [136, 137]. In two Indian studies with early relaparotomy after CS, RSH was found in 21–27% of cases [136, 137]. In Western countries, this is an extremely rare condition during pregnancy with only several case reports after CS [138–140].

11.4.4 Mechanism of Injury

11.4.4.1 Direct Trauma

Direct injuries of the IEA include *blunt trauma* [139] or *penetrating abdominal wall trauma*. Distention of the abdominal wall during pregnancy causes elongation of the inferior epigastric artery. Blunt trauma to that region possibly causes further distention of the inferior epigastric artery beyond its elastic modulus, making it prone to tears and lacerations with subsequent bleeding [141]. If delivery occurs immediately after abdominal trauma, it is not known whether the cause is abdominal trauma or the process of delivery with straining itself [132].

Penetrating abdominal wall trauma during interventions including CS, paracentesis, and insertion of trocars during laparoscopy causes direct injury to the IEA. Injuries to the ascending branch are well documented and usually occur after direct trauma to the abdominal wall, for instance, during laparoscopic surgery, subcutaneous injections, insertion of lumboperitoneal shunts, or ascites fluid aspiration. In one of the Indian studies, 95.5% of patients with injury of IEA had intrapartum CS, while 4.5% had an elective operation. Therefore, emergency CS is a risk factor for IEA bleeding [136]. During CS, care during transverse cutting and suturing of the lateral extension of the rectus sheath is advised [137].

11.4.4.2 Spontaneous

The condition occurs mainly in multipara and late in pregnancy. It has also been described in puerperium and even within half an hour of delivery and expulsion of the placenta. In almost all cases in pregnancy, there was some evidence of trauma from labor, from coughing, or from a fall. Muscle degeneration from influenza or typhoid is a possible cause. The precipitating factor in most spontaneous cases seems to be inelasticity of the wall of an artery or vein which prevents the vessel from accommodating itself in a movement, a cough, or a sneeze or, in or after labor, to the remarkable variations in length which the rectus muscle undergoes between extreme contraction and extreme relaxation. According to Brödel, there is only one major vessel to take care of this long stretch of muscle, and in order to avoid damage to itself, it must keep away from the muscle so far as possible and send its branches into the muscle substance in such a manner that the muscle action does not interfere with vascular freedom. The larger intramuscular arteries branch freely and form numerous anastomoses. They run at an angle varying from 60° to 90° to the axes of the muscle bundles. If an occasional artery runs parallel to the muscle bundle, it shows greater tortuosity. The arteries are less apt to tear than the veins because they are far more resistant. They lie and so loosely embedded in the intramuscular connective tissue that they can be pulled out quite far without injury, but not so with the veins. They are frail, of smaller caliber, and have a much thinner wall. Tears may be partial or complete. In a partial tear, only branches of the main vessels rupture beyond their point of entry into the muscle body, but a complete tear is apt to rupture the main trunk also.

Right-sided hematomas in the general population are presumably more common because more people are right handed and, thus, are more prone to the right-sided strain of the rectus muscle during strenuous activity. The lower quadrants are more frequently involved because of the long vascular branches that are present and because muscle excursion during contraction with the absence of the tendinous inscriptions is greater [134].

Rarely, the ascending branch may rupture spontaneously, most notably in patients taking anticoagulant medications, after lifting heavy weights, coughing, or straining. Thus, tearing of the branches of the epigastric vessels is a well-known cause of RSH [142].

11.4.5 Clinical Presentation

Clinical presentation depends on the severity of the injury and the timing of the incident. If observed intraoperatively and IEA itself is injured/transected, then significant bleeding is present. If the peritoneum is intact, then large subperitoneal hematoma is found. If the peritoneum is damaged, significant bleeding into the abdominal cavity from the abdominal wall is found. If the bleeding is not observed intraoperatively, then the severity of the clinical presentation depends on the caliber of the artery that is injured. If the IEA is damaged, then immediately after the operation, there will be symptoms and signs of significant blood loss and hemorrhagic shock: tachycardia, lowered blood pressure, increased pulse rate, pallor, and cold sweat. Additionally, the patient will have a distended and painful abdomen. On inspection, hematoma over the IEA is found.

11.4.5.1 Spontaneous Rectus Sheath Hematoma

A history of anticoagulant therapy and trivialities such as coughing, straining, or twisting to one

side may remind the clinicians of this diagnosis. Awareness of RSH during pregnancy is important because the abdominal wall is easily overlooked as a cause of acute abdominal pain [143, 144], given the higher prevalence of other pregnancy-associated pain.

Among the clinical findings, premonitory vague discomfort at the site of bleeding is common with the lesser degrees of hemorrhage. Probably a great number of the hematomas are small, unnoticed, and consequently unreported. In most recorded cases, the hematoma was limited to the rectus sheath, and pain and tenderness were felt over the bleeding area. Muscle rigidity is often marked in the involved rectus, but in small hemorrhages, there is little more than a local tenseness in the muscle. Swelling and palpable firm, non-pulsatile mass is usually confined to the affected muscle sheath. Swelling of the hematoma is limited to the rectus abdominis muscle, with its sheath not extending beyond the abdominal midline or the lateral borders of the muscle (*Romanzew*'*s sign*). However, below the arcuate line, the posterior sheath may communicate, and the mass may project across the midline or extend inferiorly and posteriorly toward the bladder. In some cases, the hemorrhage escaped the limits of the muscle sheath and extended into the broad ligament or ruptured into the peritoneal cavity [145].

The hemorrhage lies initially between the transversalis fascia and the posterior surface of the rectus muscle, spreading later to surround the muscle and ascend over the linea semilunaris between the rectus muscle and its posterior sheath and sometimes downward behind the rectus. If the patient lifts her head off the pillow so as to contract the rectus, the mass can be felt confined to the rectus sheath and immovable. The mass is equally palpable with the patient lying in a supine position or partially sitting up (*Fothergill*'*s sign*). Swollen and palpable mass is usually confined to the affected muscle sheath and severe, usually unilateral, abdominal pain that is aggravated by movement [146].

Carnett'*s sign* is performed by first localizing the area of maximal tenderness while the patient is relaxed. While this area is being pressed, the patient is asked to raise her upper back, effectively tensing the abdominal wall. Worsening of the pain is considered a positive test [147]. In 1926, Carnett recognized that abdominal pain could be caused by neuralgia affecting one or more of the lower six intercostal nerves and developed a simple test to help localize the origin of symptoms to the abdominal wall [148]. For this part of the abdominal examination, the patient can be asked to lift the head and shoulders from the examination table to tense the abdominal muscles. An alternative is to ask the patient to raise both legs with straight knees.

Staining of the skin and ecchymosis are very common over the palpable mass (*Cullen*'*s sign*), first described by Guthrie and Stamfey, who also found *Grey-Turner*'*s sign* with RSH [149]. These occur over the center of the hematoma, as a semicircle around the umbilicus, above the pubis, or along the linea alba (Fig. 11.11). The extravasated blood can pass more easily superficially around the medial border of the rectus. The pigments that produce this phenomenon may reach their destination by following the ordinary fascial planes but not by the lymphatics as was previously believed. In RSH, ecchymosis appears after 2–5 days.

11.4.5.2 Traumatic Rectus Sheath Hematoma

The presentation is the same as in spontaneous RSH, but additional injuries should be excluded

Fig. 11.11 Staining of the skin and ecchymosis are very common over the palpable mass not extending over the midline. Reproduced with permission from [150]

especially in high-energy trauma such as motor vehicle accidents.

11.4.6 Differential Diagnosis

Spontaneous RSH presents a significant diagnostic problem because skin changes in smaller hematomas could be absent, and the patient presents with acute significant pain with peritoneal irritation which mimics intra-abdominal conditions such as acute appendicitis, diverticulitis, cholecystitis, tumors, and visceral injuries [142]. In these situations, Carnett's sign is helpful to differentiate between the abdominal wall and intra-abdominal pathology.

11.4.7 Diagnosis

11.4.7.1 Transabdominal Ultrasound

The diagnosis of RSH should be suspected on clinical grounds and supported by additional imaging evidence. Ultrasonography often shows a heterogeneous hypoechoic mass in the abdominal wall and is most useful for detecting RSH [144]. Type III hematomas are large and could mimic intraperitoneal emergency such as torsion of the adnexa or placenta percreta with bleeding into the extrauterine compartment

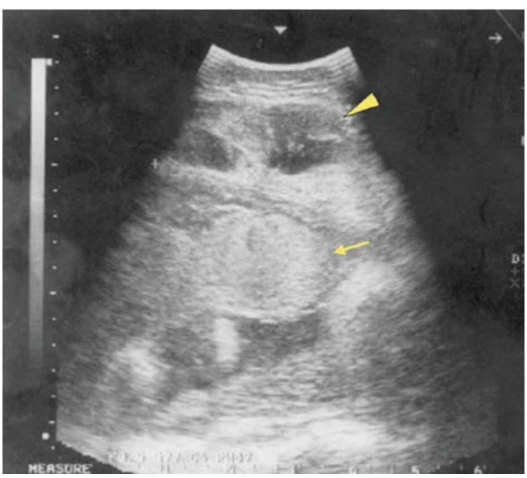

Fig. 11.12 Abdominal ultrasonography shows a heterogeneous hypoechoic mass (*arrowhead*) adjoining the placenta (*arrow*). Reproduced with permission from [151]

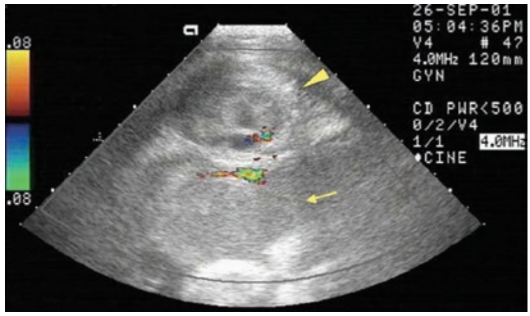

Fig. 11.13 Doppler sonography shows vascularity with blood flowing around the mass (*arrowhead*) and between the mass and the placenta (*arrow*). Reproduced with permission from [151]

(Fig. 11.12). In unequivocal cases, Doppler can aid the diagnosis showing nonvascularized structure (Fig. 11.13).

11.4.7.2 Abdominal CT

Three types of RSH in the general population can be distinguished by computed tomography appearances. *Type I* is unilateral and contained within the muscle; *type II* is uni- or bilateral and has blood between the muscle and transversalis fascia; *type III* invades the prevesical space or peritoneum and may or may not affect the muscle [152]. Until a classification in pregnancy is defined, the best option for the treatment algorithm is to adhere to the aforementioned classification.

With the improved accuracy of modern ultrasonographic equipment and also due to the fear of exposure of the fetus to radiation, the use of CT and technetium-99-labeled red blood cell scintigraphy is limited [144].

11.4.7.3 Abdominal MRI

Abdominal MRI appears to be a safe and accurate option for detecting RSH (Fig. 11.14).

11.4.7.4 Angiography

The IEA represents a potentially overlooked source of pelvic arterial hemorrhage. The IEA should be considered as a possible source of arterial hemorrhage if arteriography of internal iliac artery branches does not yield a bleeding source [139].

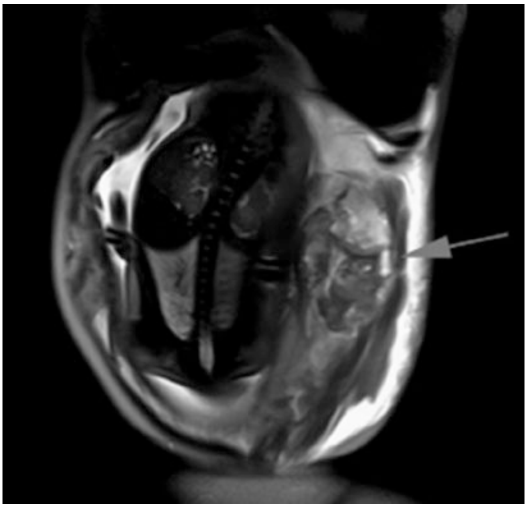

Fig. 11.14 Abdominal MRI (coronal T2-weighted) showing a large left-sided rectus sheath hematoma measuring 160 × 70 × 55 mm (*arrow*). Note the subcutaneous fat stranding and a small hemoperitoneum coexisting with a fetus of 33 weeks of gestation. Reproduced with permission from [135]

11.4.8 Treatment

11.4.8.1 Conservative Treatment

Cases of bleeding IEA after CS are never treated conservatively. On the other hand, management of RSH is guided by the size of the hematoma and hemodynamic stability of the patient. Where the hematoma was small, it usually spontaneously resolves uneventfully within 1–2 weeks, although the complete resolution of the hematoma may take as long as 2–3 months. Treatment generally consists of rest, peroral analgesia, and discontinuation of anticoagulation (if present). After resolution, RSHs usually do not recur and typically do not cause long-term sequelae.

Most patients are treated with peroral NSAIDs and/or opioids for pain relief. There is a case of transversus abdominis plane block for severe pain, eliminating large dosage of peroral pain killers [140].

11.4.8.2 Transarterial Embolization

Almost all cases of bleeding IEA after CS are treated by transarterial embolization (Fig. 11.15) [138, 139, 153]. In only one case, the patient was treated conservatively (abdominal CT was used for the diagnosis) [140].

Identification of a bleeding point is useful in guiding management; a massive hematoma that extends into the retroperitoneum may originate from a bleeding inferior epigastric vessel or may be coming from a retroperitoneal structure such as a leaking iliac or abdominal aortic aneurysm. Selective percutaneous transcatheter arterial embolization is considered an effective hemostatic for large RSH [135]. With regard to the safety of embolization during pregnancy, the generally late onset of this pathology reduces the risks associated with fetal irradiation. The large RSH displaces the uterus and the fetus to the contralateral side, reducing the dose of X-rays delivered to the fetus [135]. Selective epigastric embolization in severe RSH during the third trimester of pregnancy should be considered as the potential primary and alternative management path to classical laparotomy. However, this technique is time-consuming, expensive, and not always available. This procedure is also associated with complications such as contrast-induced nephropathy or bleeding from the puncture site. Another disadvantage is that the bleeding vessel cannot always be identified. Further studies are required to confirm that the maternal and fetal benefits outweigh the fetal risks associated with embolization.

11.4.8.3 Surgical Treatment

In cases with rupture into the peritoneum, infection, or active bleeding with unstable hemodynamics, prompt surgical intervention is indicated. If the hematoma is very extensive and when the shock is controlled, a paramedian incision with a section of the rectus sheath and retraction of the muscle laterally will facilitate visualization of the bleeding vessel. The suture of the ruptured vessel or muscle should be performed. If the rupture is intraperitoneal, laparotomy is indicated to evacuate blood and clots and to control bleeding. If the infection is present, evacuation of purulent material is mandatory with bacterial swabs and drains left in place.

11.4.9 Prognosis

11.4.9.1 Spontaneous Rectus Sheath Hematoma

In Maxwell's series of 11 patients, eight were during pregnancy with 0% maternal mortality and

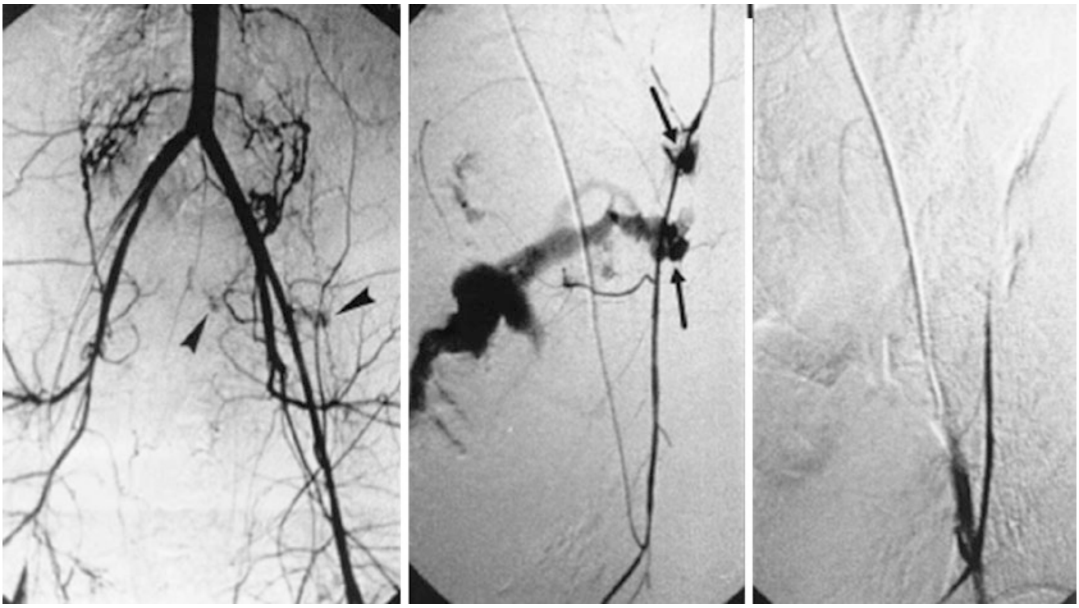

Fig. 11.15 (*Left*) Aortoiliac arteriogram showing suspicious abnormal stains (*arrowheads*) on the left side of the pelvis. (*Middle*) selective left inferior epigastric arteriogram showing massive bleeding from two injured portions (*arrows*). (*Right*) complete occlusion of bleeding points after embolization. Reproduced with permission from [138]

37.5% fetal mortality (additional two of eight cases do not mention fetal outcome). Three spontaneous RSHs during labor resulted in 0% maternal and fetal mortality. In Torpin's series, there was a 15% maternal mortality and a 50% fetal mortality [133]. Reports from the 1950s show a maternal mortality of 12% and a fetal mortality of 25%. In 1997, the maternal mortality rate of 11% and a perinatal morbidity rate of 34% were reported [143].

11.5 Omental Infarction

11.5.1 Incidence

Omental infarction is a rare clinical event that affects predominantly young and middle-aged women [154]. Omental infarction was first reported in 1882 by Oberst [155], and since then up to 1986, only a few hundred cases have been published in the English literature [156]. Almost all published cases describing omental infarction are in the postpartum period—both after CS [157, 158] and vaginal deliveries [159, 160]. Cases during pregnancy present in the second half of pregnancy [161, 162].

11.5.2 Etiology

Torsion of the omentum in the general population is the main reason for infarction, and two different forms have been described: primary torsions (without other pathologic intra-abdominal findings) and secondary torsions (tumors, cysts, inflammatory changes, adhesions, hernias). Predisposing factors for torsion are anomalies of the omentum, such as a small root, irregular vascular anatomy, abdominal trauma, cough, and physical strain [155]. Depending on the duration and the degree of torsion, omental necrosis ensues (Fig. 11.16).

The etiology of omental infarction without torsion remains uncertain, but several mechanisms have been proposed, such as an anomaly of the venous vessels [163]. Other possible causes for primary infarctions could be disorders of hemostasis or vascular diseases exaggerated during pregnancy and puerperium when

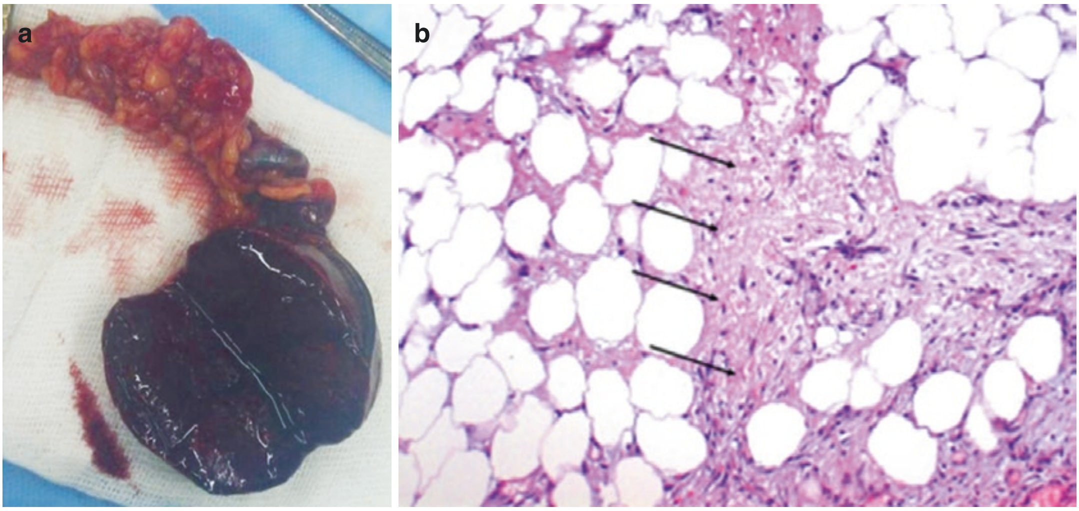

Fig. 11.16 (**a**) Torsion of a right lower segment of omentum resulting in omental gangrene. Reproduced from [161] under the CC BY 3.0. (**b**) Histological findings of major omentum show fresh hemorrhagic circulation disorders (*arrows*), partial necrosis of fatty tissue with acute inflammatory cell infiltrate (hematoxylin, ×100). Reproduced from [159] under the CC BY 2.0

hypercoagulability leads to an increased risk of thromboembolic events [164].

The exact mechanism leading to infarction in puerperium remains unclear. Possible increase in intra-abdominal pressure during labor, a high decrease of uterine volume immediately after the labor, and the return of the mother's body to the prepregnancy physiological condition may have provoked the torsion.

11.5.3 Clinical Presentation

Usually, the clinical symptoms of an omental infarction are localized peritoneal irritation on the right side of the abdomen. The patient can be afebrile [159, 162] or sometimes associated with low-grade fever when omental necrosis develops.

11.5.4 Differential Diagnosis

The clinical picture often misleads physicians to assume an incorrect preoperative diagnosis (Table 11.4).

Table 11.4 Differential diagnosis of omental torsion during pregnancy [157, 159, 162]

Acute cholecystitis
Acute appendicitis
Colonic diverticulitis
Appendagitis epiploica
Incarcerated umbilical hernia
Adnexal torsion
Myocardial infarction

11.5.5 Diagnosis

11.5.5.1 Laboratory Findings

The C-reactive protein and white blood count may be elevated [159], depending on whether the (partial) necrosis of the omentum occurred.

11.5.5.2 Abdominal CT

As most patients show symptoms of an acute abdomen, CT of the abdomen and pelvis should be the diagnostic imaging of choice in the general population [165]. If omental infarction is caused by torsion, characteristic CT findings might be detectable. The torsion leads to the presence of concentric linear strands in the fatty mass, a so-called *fat spiral pattern* (Fig. 11.17).

Fig. 11.17 CT scan of the abdomen showing a hypoperfused mass in the anterior portion of the median epigastrium with fatty density (*white arrows*) and a thin layer of free fluid surrounding the liver. Reproduced from [159] under the CC BY 2.0

Differentiating the omental infarction from other abdominal or omental diseases is challenging, and the radiological findings could be misinterpreted as a incarcerated umbilical hernia [159].

11.5.5.3 Diagnostic Exploration

Diagnosis of an omental infarction has traditionally been made intraoperatively during an exploratory laparotomy or laparoscopy, and the treatment has been partial or total omentectomy. If there is another pathology, it should be treated during the exploration.

11.5.6 Treatment

11.5.6.1 Conservative Treatment

Recent reports highlight cases of patients with CT-diagnosed omental torsions who have been successfully treated conservatively without any other complications (such as bacterial superinfections) [166, 167]. Whenever conservative treatment fails or the clinical status of the patient worsens, a surgical intervention should be quickly implemented.

11.5.6.2 Surgical Treatment

Due to unspecific clinical findings, surgical exploration leads to the diagnosis. All parts of the omentum that are macroscopically changed should be resected to eliminate the possibility of recurrent torsion and infection that can supervene omental necrosis.

11.5.7 Prognosis

Prognosis is excellent. Fetal outcome is rarely influenced by the disease because most cases present during puerperium. Two cases during pregnancy had uncomplicated delivery with healthy newborns [161, 162]. The maternal outcome is also excellent due to the benign nature of the primary disease [157, 159].

11.6 Gastrointestinal–Genital Communications

11.6.1 Introduction

In some cases, it is more precise to define the pathologic process as communication or even infiltration than fistula due to the close contact of gastrointestinal and genital organs that produce symptoms even without a true channel between them.

11.6.2 Incidence

Communication of the gastrointestinal tract with the genital system from any cause is an unusual occurrence. Up to 1956, 80 cases of enterouterine fistula were collected—52.5% followed an obstetric injury [168]. In a review of over 1000 consecutive cases of ectopic pregnancy at the Cook County Hospital (1940–1956), Webster and Kerr found only one associated with bowel invasion [169]. Enteroamniotic fistulas resulting from complications of ectopic pregnancy are even more unusual, only occasional cases being published. Cases presenting with rectal hemorrhage or melena from an unknown source ultimately proved to have arisen from rupture of an ectopic pregnancy into the bowel are presented in Table 11.5. The first known case is by Armstrong,

Table 11.5 Rectal hemorrhage or melena with ectopic pregnancy

Author	Year	Site of ectopic pregnancy	Presentation	Perforation site	Treatment	Maternal outcome
Armstrong [170]	1835		Rectal bleeding			Dead
Edgar [171]	1901	Unknown	Rectal bleeding	Sigmoid colon	Posterior colpotomy	Dead
Webster and Kerr [169]	1956	Right interstitial	Rectal bleeding	Terminal ileum and appendix	Resection of ileum, ileoileostomy, appendectomy, right salpingectomy, wedge resection of right uterine corn	Dead
Engel [172]	1961	Left interstitial	Rectal bleeding	Mid ileum	None	Dead
Shirkey et al. [173]	1963	Left interstitial	Rectal bleeding	Terminal ileum	Suture ileum, total abdominal hysterectomy, left salpingectomy, right salpingo-oophorectomy	Alive
Bigg et al. [174]	1965	Right interstitial	Rectal bleeding	Cecum	Supracervical hysterectomy, right salpingo-oophorectomy, tube cecostomy	Alive
Patterson et al.			Rectal bleeding	Cecum		
Rudik et al. [175]	1978	Tubular	Rectal bleeding	Sigmoid colon		
Bornman et al. [174]	1985	Abdominal	Rectal bleeding	Sigmoid colon	Removal of the placenta, sigmoid resection with anastomosis and proximal loop colostomy	Alive
Aberto et al. [176]	1985	Abdominal	Rectal bleeding	Terminal ileum	Right adnexectomy, ileal resection with anastomosis, removal of the fetus and placenta	Alive
Seow et al. [177]	1992	Abdominal	Rectal bleeding	Cecum		
Saravanane et al. [178]	1997	Abdominal	Rectal bleeding	Rectum	Removal of the fetus and placenta, transverse colostomy	Alive
Ekwaro et al. [179]	2004	Left tube	Rectal bleeding	Sigmoid colon	Left salpingectomy, suturing of sigmoid perforation	Dead
Machado [180]	1974	Abdominal	Melena			
Kulunga et al. [181]	1984	Interstitial	Melena	Terminal ileum	Removal of the placenta, suturing of ileal perforation	Alive
Iwagaki et al. [182]	1991	Tubular	Melena	Terminal ileum	Ileocecal resection, right salpingectomy	Alive?

in 1835, of a woman in her sixth month of pregnancy who suddenly passed bloody stools containing fetal bones and died of hemorrhage [170].

11.6.3 Etiopathogenesis

11.6.3.1 Enterouterine Fistula

Le Jemtel, in 1909 [183], presented an etiological classification of enterouterine fistulas updated by Hawkes [184]. There are four major etiological categories:

- Cancer—by infiltration and invasion arising in either the bowel or uterus
- Peritonitis—from trauma, puerperal infections, intestinal inflammation, and fistulas following abscess formation involving the inflamed adjacent walls of both the uterus and intestine
- Traumatic or spontaneous rupture of the gravid uterus with strangulation of a loop of bowel caught in the defect
- Perforation of the uterus and bowel at the time of curettage

11.6.3.2 Enteroamniotic Fistula

Extrauterine/Abdominal Pregnancy

Stock, in 1944, has described the role of infection in a case of secondary abdominal pregnancy complicated by fistula formation and rupture through the umbilicus [185]. The approximation of a vascular placenta, with the potential of villous invasion of adjacent structures, to the intestine, creates a precarious set of circumstances. Following the villous invasion of the bowel wall, on the approximation of the gestational sac to the intestine, inflammatory reaction and infection may create fistula formation. The source of infection may vary according to the location of the ectopic sac. Intraperitoneal ectopic sacs are most commonly infected from the adjacent bowel, whereas intraligamentary sacs are most often contaminated by bacteria from the vagina or uterus [185]. The vascular gestational structures aggravated by infection and villous invasion of adjacent vascular structures provide a dangerous source of massive hemorrhage (Fig. 11.18).

Similarly, following the villous invasion of the bowel wall, the infection can occur in the gestational sac as a result of a fistula formation between the sac and the bowel [173].

Gastrointestinal Inflammation

The most common cause is inflammatory bowel disease in a form of Crohn's disease [186].

Obstetric Cause

The two most common causes of enterouterine fistula are CS (Fig. 11.19) and endoluminal uterine instrumentation, most commonly in a form of instrumental abortion or curettage for any obstetric cause [187].

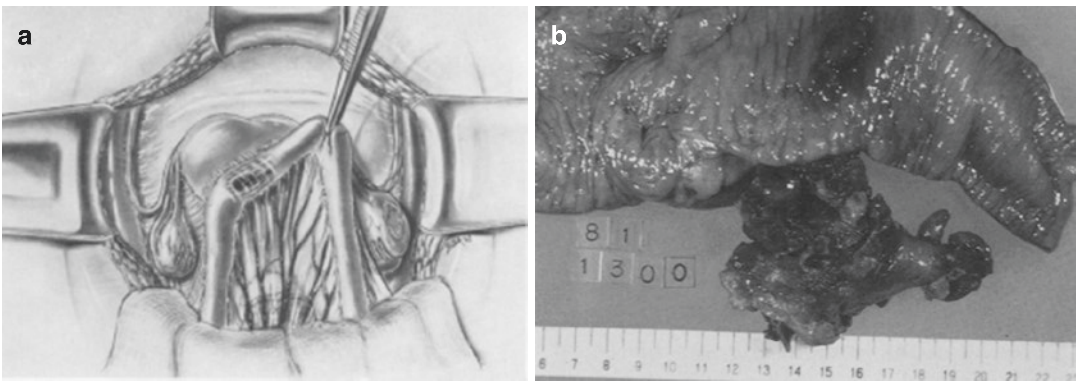

Fig. 11.18 (**a**) Terminal ileum firmly attached to the left cornu of the uterus with a fistula between ectopic gestation and small bowel wall with lumen exposed. Reproduced with permission from [173]. (**b**) Terminal ileum with a perforated lesion of 5 × 4 cm and the Fallopian tube pregnancy constituted by blood clots in which small areas of yellowish villous material are present. Reproduced with permission from [182]

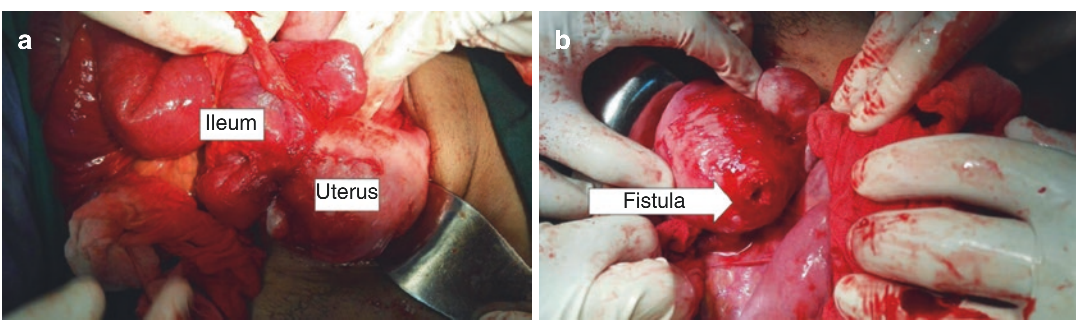

Fig. 11.19 (**a**) Small bowel adherent to the posterior wall of the uterus. (**b**) The ileo-uterine fistula observed after separation of the bowel loops. Reproduced with permission from [188]

11.6.4 Prevention

The importance of meticulous surgical technique in reperitonealization of the pelvic floor, uterus, and Fallopian tubes and in the manipulation of the bowel is stressed by Engel [172]. This case, documented by careful postmortem examination of involved structures, illustrates how inadequate reperitonealization of the uterus during a previous ipsilateral salpingo-oophorectomy allowed a loop of the ileum to become adherent to the uterus. This set of circumstances made perforation of the adjacent ileum by a subsequent interstitial pregnancy a more likely possibility, ultimately costing the patient her life due to profuse hemorrhage into the bowel from an intrauterine vessel.

11.6.5 Clinical Presentation

Depending on the advancement of pregnancy, location, type, genital and end gastrointestinal organ, the clinical presentation is different. Hours to days after instrumental abortion the patient with enterouterine fistula commonly presents with passing the semiformed fecal matter through the vagina. If there are no signs of peritonitis or partial/complete bowel obstruction, this is the only symptom [189].

Expulsion of fetal parts or disintegrated fetal bones per rectum indicates a fistulous tract between the genital tract (or anywhere in the abdomen in extrauterine pregnancy) and the gastrointestinal tract [190].

Rectal bleeding can be the only sign in the rectosigmoid location of infiltration or perforation [178]. Depending on the severity and duration of bleeding, the patient can present in severe hemorrhagic shock or just show signs of bleeding as being pale [174]. Ectopic pregnancy as the cause should be suspected when simultaneous or sequential vaginal and rectal bleeding is present [174]. Another clue to the diagnosis of ectopic pregnancy as a cause of rectal bleeding is the sequence of symptoms [174, 177, 178]:

- Amenorrhea
- Lower abdominal pain
- (Vaginal bleeding followed by) Rectal bleeding

Instead of rectal bleeding, the patient can present with melena, and also fetal parts could be found protruding through the anus [191] or bowel wall during the proctoscopic or colonoscopic examination. Vaginal bleeding can precede abdominal pain [182].

11.6.6 Diagnosis

The high mortality rate associated with cases causing hemorrhage indicates the seriousness of perforation of the vascular gravid genital system into the intestinal tract, the need for suspicion of the condition, and the knowledge of the principles essential for successful management.

11.6.6.1 Endoscopy

If the bleeding is in the rectum, the proctoscopic examination can reveal a bleeding or a defect in the anterior wall of rectal mucosa sometimes with evidence of active bleeding [178]. If proctoscopic examination does not reveal the site of hemorrhage or the blood comes from upper portions of the colon, sigmoidoscopy [174] or colonoscopy should be performed.

11.6.6.2 Hysterosalpingography

Hysterosalpingography can reveal the communication with the gastrointestinal tract. The contrast put through the cervix into the uterine cavity is clearly seen in the bowel loops (Fig. 11.20).

Fig. 11.20 Absence of opacification of the uterine cavity and beginning of opacification of the bowel loops. Reproduced with permission from [187]

11.6.7 Treatment

> Unlike in the general female population, gastrointestinal–genital communications (fistulas) represent true emergency due to deleterious consequences to the fetus itself and normal progression of pregnancy.

Early laparotomy and minimal surgery on the involved bowel are the key factors in improving the maternal survival rate.

11.6.7.1 Gastrointestinal–Genital Fistula

Knowledge of the possibility of fistula formation between an ectopic gestational sac and bowel and suspicion of its presence is essential for successful management. Intestinal hemorrhage in any potentially pregnant woman should stimulate consideration of this dangerous condition. Consideration of the role played by an inevitable presence of infection in these cases makes necessary the complete excision of all involved structures when possible [192]. When technically feasible, all structures, including the uterus, should be excised when involved in the infected fistula and inflammatory process (Fig. 11.21).

11.6.7.2 Abdominal Pregnancy

Exception from the previous rule of complete excision is the abdominal pregnancy, where the extensive intimate invasion of the surrounding structures by the placenta makes removal dangerous and usually impossible. Surgery in the setting of abdominal pregnancy with bowel invasion is more hazardous than in uncomplicated abdominal pregnancy where the placenta can be left undisturbed even though the vascular supply of major organs is involved (see Sect. 15.3.7.2). Even in this situation, consideration should be given to resection of as much involved tissue as possible with drainage in an attempt to prevent intra-abdominal abscess formation. In simple fistula formation with only a small opening into the intestine and absence of marked inflammatory reaction, simple closure of the bowel is acceptable. Otherwise, in the emergent setting, segmental resection with end-to-end anastomosis in the case of the small bowel and right colon, or diverting procedure in the involvement of the left colon and rectum, is indicated.

11.6.8 Prognosis

Up to 1961, the mortality of ectopic pregnancy causing rectal bleeding or melena was 100% due to hemorrhagic shock, delay in diagnosis and

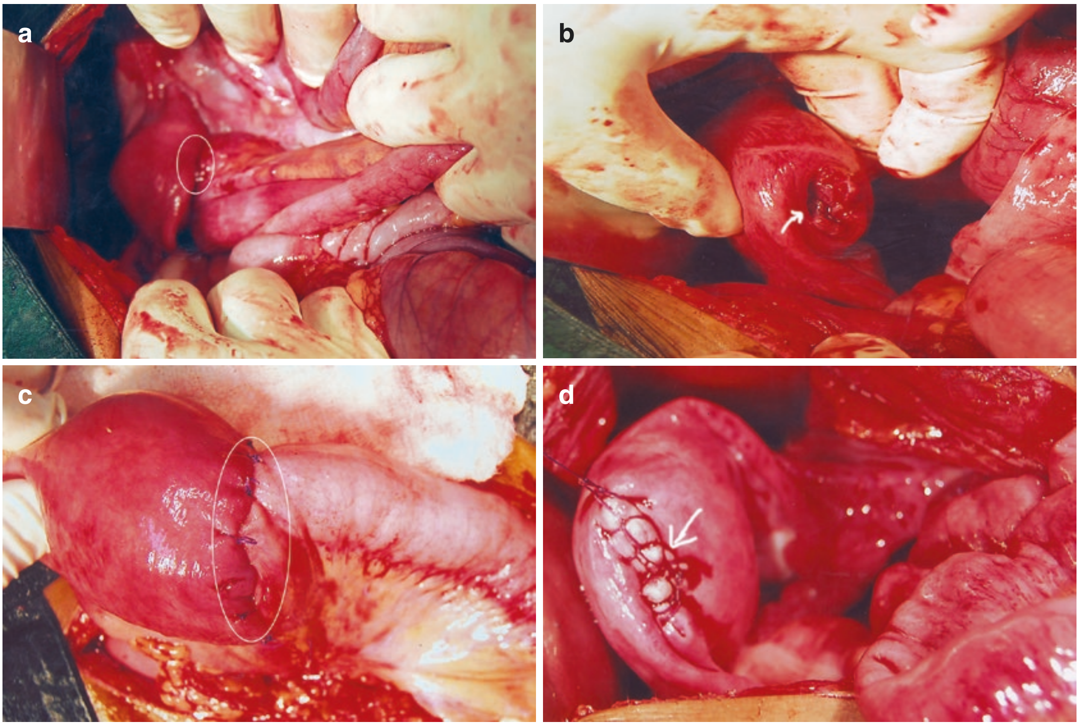

Fig. 11.21 (**a**) Ileal loop adherent to the fundus of uterus posteriorly; (**b**) perforation of uterine fundus posteriorly near left cornu; (**c**) resection with ileal end-to-end anastomosis (note the dilated proximal ileal loop); (**d**) closure of uterine perforation in two layers. Reproduced with permission from [189]

treatment, resection of the involved segment of the bowel, and its potential complications [169–172]. After 1961, maternal survival is more than 90%. It is even higher in developed countries because deaths are reported from undeveloped countries (Table 11.5).

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Part II

Gynecology

12 Adnexal Torsion

Abstract

Adnexal torsion is one of the most common nonobstetric, but gynecologic, acute abdominal conditions in pregnancy. Due to the growing uterus, adnexa are pushed from pelvic to an abdominal position making them more prone to torsion. Today, with more widespread use of assisted reproductive technologies that result in ovarian hyperstimulation syndrome, adnexal torsion is even more common. Due to the often nonspecific clinical presentation, differential diagnosis is wide with some differential diagnoses that are side-specific. Sonography has high sensitivity and specificity for the diagnosis, and abdominal MRI is used in unequivocal cases. The treatment is operative. An additional reason for early operative detorsion is ovarian salvage in early pregnancy which hormonal role is important for the normal advancement of pregnancy.

12.1 Introduction

When a pregnant woman has a violent diarrhea, there is danger of her miscarrying in a pregnant woman, if the breasts suddenly lose their fullness, she has a miscarriage.

If, in a woman pregnant with twins, either of her breasts lose its fullness, she will part with one of her children; and if it be the right breast which becomes slender, it will be the male child, or if the left, the female.

When women, in a moderate condition of body, miscarry in the second or third month, without any obvious cause, their cotyledons are filled with mucosity, and cannot support the weight of the fetus, but are broken asunder.

In women that are about to miscarry, the breasts become slender; but if again they become hard, there will be pain, either in the breasts, or in the hip-joints, or in the eyes, or in the knees, and they will not miscarry.

Women with child who are seized with fevers, and who are greatly emaciated, without any (other?) obvious cause, have difficult and dangerous labors, and if they miscarry, they are in danger.

Hippocrates, 400 BC

Evaluation of a patient during pregnancy who presents with acute abdominal pain should always include a search for surgical and gynecologic disorders. Parsons in 1958 stated that 40% of women in general population who present with symptoms of pain in the lower abdomen and pelvis do not have the gynecologic disease [1].

Preservation of reproductive capability (childbearing, hormonal function, and sexual health) has a major impact on the wellness of a woman. This important issue should be considered in the surgical management of acute gynecologic problems.

Adnexa refers to the anatomical area adjacent to the uterus and contains the Fallopian tube, ovary, and associated vessels, ligaments, and connective tissue. *Adnexal torsion* (AT) is defined as total or partial rotation of adnexa around its vascular pedicle resulting in ischemia.

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_12

12.2 Historical Perspective

First descriptions of AT was by Morgagni in 1748 and Rokitansky in 1850. Ovarian torsion (OT) in nonpregnant female was first described by Kuestner in 1891 [2]. Green-Armytage in 1929 and Sheldon in 1936 reported cases of torsion of both the Fallopian tube and the ovary during pregnancy [3, 4]. In 1909, Gifford Nash published a case of isolated torsion of paraovarian cyst during early pregnancy [5] and Fleming in 1920 an ovarian cyst in the fifth month of pregnancy [6], both without AT. Due to the adherence and size of the ovarian cyst, Fleming resected the involved left Fallopian tube.

12.3 Incidence

AT in general female population accounts for 2.5–7.4% of all gynecological emergencies [7, 8], while others claim AT is the 5th most common gynecological emergency [9]. This prevalence is probably underestimated because a significant number of patients with OT are not diagnosed because they were not operated, mostly due to spontaneous detorsion [10, 11] or ovarian autoamputation without further symptoms or complications (Fig. 12.1). Cysts found in pregnant women on sonography very rarely (3.8%) result in torsion [12]. The overall prevalence of AT in pregnancy is 1/5000 [13]. Isolated maternal OT during pregnancy is a rare event, with a reported incidence of 1-10/10,000 spontaneous pregnancies [14–16].

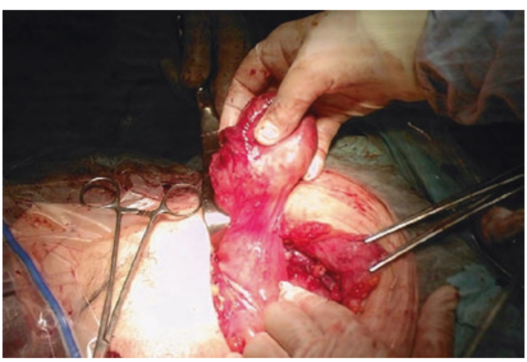

Fig. 12.1 Macroscopic appearance of incidentally found autoamputated ovary in the cul-de-sac during Cesarean section for the lack of progress in labor. Reproduced with permission from [17]

Torsion of hydatids of Morgagni involving the ipsilateral Fallopian tube has been advocated as a cause of acute abdominal pain in adolescents, being involved in about 25% of ATs in this subgroup. However, the condition is uncommon in the adult female [18], representing a marginal part of ATs and very rarely reported during pregnancy (see Chap. 13).

However, AT has been reported to occur in 7–28% of all pregnancies complicated by adnexal masses [7, 19–23]. AT is an important concern of pregnancy-associated adnexal masses and had a much higher incidence (13.8%) than malignancy (3.4%) [24]. The reported incidence of adnexal tumor torsion varies widely, ranging from 0.8% [25] to 53.8% of tumors undergoing antepartum surgery [26].

In an 80-year review, Jubb collected only 34 cases of ovarian cancer associated with pregnancy [27]. In 1973, Munnell also emphasized the infrequent association of ovarian cancer and pregnancy at 1/18,000 pregnancies [28]. More recent comprehensive reports summarized the incidence of 0.18–2.8/10,000 pregnancies [29, 30]. It is uncertain whether the incidence of ovarian cancer associated with pregnancy is rising. However, since the age of childbearing among older women increases, the incidence of cancer is also likely to rise in pregnancy. In one study of 12 years' experience, 98% of cases were elective with only one emergent operation for AT [31]. Bilateral torsion, either simultaneously or sequentially, is infrequent, with few cases reported in the literature [32, 33].

AT with adnexal mass may occur at any time during gestation, although its incidence decreases as the gestational age increases [14, 32, 34]. In contrast, torsion of the normal adnexa during pregnancy or the postpartum period is uncommon, and the true incidence of such a rare condition is unclear.

12.4 Risk Factors

Due to the effect of inertia, most torsions are due to some underlying adnexal pathology or normal or pathological hyperfunction.

12.4.1 Adnexal Mass

Depending on the method and definition of a clinically significant adnexal mass, the prevalence of pregnancies complicated by an adnexal mass is 1–8% [9, 35–37]. A small percentage of these, approximately 5%, will represent malignant tumors, making ovarian cancer the fifth most common cancer diagnosed during pregnancy (see Chap. 14) [38]. The incidence of simple or complex ovarian cyst in pregnancy is reported as 5–8%, of which 0.7–3% can undergo torsion [9, 39]. The incidence of histopathologically confirmed ovarian tumors during pregnancy is presented in the Table 12.1. The most common tumor during pregnancy is benign cystic teratoma (22–40% of all ovarian tumors) [40]; therefore, it is most common tumor found during AT. Torsion occurs in 19% and rupture in 17% of mature cystic teratomas in pregnancy [41]. Complete torsion causes venous and lymphatic blockage leading to stasis and venous congestion, hemorrhage, and necrosis. The cyst/tumor becomes tense and may rupture. It is not known whether the type of the tumor has a predilection for isolated tumor torsion or AT in pregnancy.

> Adnexal masses with sizes 6–8 cm have a significantly higher risk of torsion [24].

A possible explanation could be that larger ovarian mass, due to the mass effect, hardly goes into torsion. Sixty percent of torsions occur between the 10th and 17th weeks of gestation, and only 5.9% after 20 weeks [24]. All AT in postpartum period occurred after 3 weeks [24]. The reason is unknown. Probably the women start to move, bend, and lift more. Sudden movement/rotation is known risk factor for AT. Tumors with larger diameters could undergo torsion during the 10–17th week of gestation, likely because the adnexal tumor had been carried out of the pelvic cavity by the gravid uterus and had a larger surrounding environment. Although the gravid uterus generally experiences dextrorotation, the incidence of torsion is not different between adnexal sides [24].

12.4.2 Anatomic Variations of Adnexa

There are cases of torsion of normal ovaries. The causes of torsion may be hypermobile ovarian ligaments, long ovarian ligaments, or other inherent ovarian mobilities. Other factors may operate to cause torsion of normal adnexa during the second trimester of pregnancy [42]. The relative situation of the adnexa and the uterus (i.e., the ovaries emerging from the pelvis by the increasing size of the uterus) may predispose the ovaries to twist by allowing them a greater mobility [43]. The main histopathologic findings in both groups were cysts of the follicular or corpora lutea [44].

AT can occur even in the normal-appearing ovary without predisposing factors [45–47]. Proposed mechanisms include abrupt changes in intra-abdominal pressure with vomiting and coughing, adnexal venous congestion during pregnancy, and sudden acceleration/deceleration movement.

12.4.3 Assisted Reproductive Technologies

The increased use of assisted reproductive technologies (ART) such as controlled ovarian hyperstimulation, in vitro fertilization (IVF), and intracytoplasmic sperm injection has led to an increase in the risk of AT, particularly when ovarian hyperstimulation syndrome (OHSS) develops. The risk of AT in OHSS is increased due to the bilaterally enlarged ovaries with multiple follicular or lutein cysts in hyperstimulated patients, especially in those who become pregnant with persistent cysts. There is no side predilection [48], and even bilateral ATs were described [48, 49].

Reported incidence in nonpregnant women with OHSS is 2.3% and 16% in pregnant women with OHSS [25]. However, 12–25% of all ATs occur in pregnant women, often in combination with assisted reproduction and its complications (OHSS). The reported incidence is low for oocyte donation cycles (0–0.2%) and IVF cycles (0–0.13%); however, the incidence increased to 6% under stimulation for ART and to 16% with OHSS [12, 13, 25, 50–54]. But even when AT occurs simultaneously with OHSS, the reported incidence varies between 1 and 33% [32]. Seventy percent of torsions occur in multiple pregnancies [50, 51, 55]. The incidence when fresh embryo transfer is done is 0.35% [56]. There are cases with OHSS treated successfully, but in the more advanced pregnancy, patients developed AT [50].

12.4.4 Pregnancy and Trimester

Pregnancy itself is a risk factor for (recurrent) AT or isolated OT without ovarian mass, despite the method of conception, and gestational age at the time of torsion. Recurrent torsion is more frequent in multicystic ovaries [14, 34]. The risk of OT rises by five times during pregnancy [24], and prevalence decreases in late pregnancy [13], as well as isolated OT [14, 15]. Ectopic pregnancy can also be found even on the contralateral side of a patient presenting with AT [57].

The majority of ATs occur in the first or second trimester of pregnancy with only 10% in the third trimester [13, 25, 45, 56, 58–60].

> Eighty percent of AT in pregnancy is on the right side [56].

The puerperal patient is more prone to the development of AT because of the rapid anatomic changes in the pelvis, accompanied by the involution of the uterus while the utero-ovarian ligament remains disproportionately stretched, thereby allowing the normal-sized ovary increased room to move and twist. This is most common during the first postpartum week [47, 61].

12.5 Clinical Presentation

12.5.1 Medical History

The presenting complaint of AT is abdominal pain, in more than 80% of patients abrupt in nature, very severe, in the right or left lower abdominal quadrant, with no relieving factors [62, 63]. It is often described as sharp and "knife-like," although it can be colicky in nature and persists less than 24 h before the patient seeks medical attention [25, 64, 65]. Abdominal pain is usually followed by nausea and vomiting (85%) in the general population [62]. The pain is proportional to the degree of circulatory obstruction; that is, complete obstruction interrupting venous return results in sudden severe pain with nausea and vomiting developing rapidly. In addition to abdominal pain, flank pain is commonly present [51, 61], and the pain may radiate to the back or groin. There may be a history of waxing and waning pain if the adnexa have been twisting and untwisting or have undergone partial torsion, causing vascular slowdown but not thrombosis [25, 54, 66]. The infundibulopelvic ligament may twist and untwist by itself, reducing and increasing the pain. There may also be a history of some jarring or movement that has caused the torsion, such as exercise before the onset of the pain or even just turning over in bed. Patients could have adnexal masses diagnosed before or even during pregnancy. Commonly, there is no history of vaginal bleeding or discharge, diarrhea, constipation, fever, or urinary complaints.

12.5.2 Physical Examination

Signs of peritoneal irritation, which are considered fundamental for the diagnosis, are present in 43% of the pregnant women and 19% of the nonpregnant women [14, 32, 67]. Pelvic examination usually reveals a tender mass on the affected side. If the patient had normal adnexa before the torsion, she might not have a mass present until later in the course of the torsion when edema and swelling of the adnexa have set in. Therefore, serial examinations may be necessary for a patient suspected of

Table 12.1 Differential diagnosis of right-sided and left-sided adnexal torsion (side differences in *italic*)

Right-sided	Left-sided
Renal colic	Renal colic
Renal or urethral calculi/obstruction	Renal or urethral calculi/obstruction
Ectopic/heterotopic pregnancy	Ectopic/heterotopic pregnancy
Hemorrhagic/corpus luteum cysts	Hemorrhagic/corpus luteum cysts
Pyosalpinx/hydrosalpinx	Pyosalpinx/hydrosalpinx
Pelvic inflammatory disease	Pelvic inflammatory disease
Ovarian hyperstimulation syndrome	Ovarian hyperstimulation syndrome
Nonpregnant horn of bicornuate uterus	Nonpregnant horn of bicornuate uterus
Bowel obstruction/perforation	Bowel obstruction/perforation
Periappendicular abscess/infiltrate	*Sigmoid diverticulitis/abscess*
Meckel's diverticulitis	
Ileocolic Crohn's disease	
Ovarian vein thrombosis	

AT. The pain is usually lower in the case of an ovarian cyst with a twisted pedicle than that found in acute appendicitis. It is of a more continuous character and followed early by a mass that increases in size quite rapidly. Only rarely will patients have evidence of abdominal guarding or rebound tenderness on physical examination. A low-grade fever may occur, but significant fevers are unlikely and, if present, may point to another cause of the pain. In a general female population with AT, it is present in only 18% [62]. Tachycardia with normal blood pressure and pulse and normal temperature indicates noninflammatory condition [68]. The extent of hemorrhage is dependent on the degree and duration of torsion, with hemorrhagic infarction occurring at a later stage but never with a large amount of hemoperitoneum. Bimanual examination defines mass felt through the fornix that is separately felt from the uterus. Tenderness is present, and mass is not moving with movements of the cervix. If not advanced pregnancy, the cervix is closed without signs of bleeding or discharge. In advanced pregnancy, dilation of the cervix can be present. Patients can present with preterm labor in addition to abdominal pain [50].

12.6 Differential Diagnosis

AT should always be considered as part of the differential diagnosis of acute pelvic/abdominal pain in women, especially those with pelvic masses diagnosed by examination or ultrasonography. The differential diagnosis differs for right-sided and left-sided AT mostly due to surgical conditions (Table 12.1) [63, 65, 69]. Gynecologic/obstetric and urologic differential diagnoses are the same for both sides. The differential diagnosis of AT is particularly difficult in combination with OHSS, as abdominal pain, nausea, and vomiting can be presenting symptoms of hyperstimulation or pregnancy itself and because the abdomen is already distended and tender because of the enlarged cystic ovaries [66]. Low-grade fever can accompany AT, but if significant fever is present, then inflammatory conditions such as tubo-ovarian abscess, pyosalpinx or pelvic inflammatory disease (see Chap. 19), or nonobstetric inflammatory conditions should be suspected.

12.7 Diagnosis

12.7.1 Laboratory Findings

Leukocytosis may be present but is also not very predictive; in a general female population, it is present in 56% of cases [62]. During pregnancy mild leukocytosis can be present; however, while levels may be increased in nonpregnant women, these may be within normal ranges for pregnant women [32, 64, 65].

Leukocytosis is also one of the laboratory indicators that may change with OHSS. If necrosis and infection of the twisted organ occur, then higher fever and higher (or progression of) leukocytosis may be present. βHCG should be routinely checked in suspected or proven cases of AT because pregnancy is a risk factor for AT (see Sect. 12.4.4) and if additional risk factors for ectopic pregnancy are present (see Chap. 15).

Hemoglobin/hematocrit is normal, but if the long-standing torsion is present or the patient is observed for 12–24 h, then a small decrease in values can be observed due to transudation of the blood-stained fluid or (hemorrhagic) cyst rupture [46]. Also, hemorrhagic infarction can occur at a later stage.

12.7.2 Transvaginal Ultrasound

When AT is suspected, a transvaginal ultrasound is indicated and may often show enlargement of the ovaries and polycystic changes without this being evidence of torsion. It is extremely rare for AT to occur with a mass less than 5 cm in diameter [56, 70]. Nonetheless, sometimes a large mass might be missed in the third-trimester presentations when the adnexa can be hidden by a large uterus. Because of varying degrees of ovarian arterial, venous, and lymphatic occlusion with torsion, the ovarian parenchyma is initially congested (Fig. 12.2), and hemorrhagic infarction occurs later [20, 71]. Sonographic findings associated with the diagnosis of AT include a predominantly

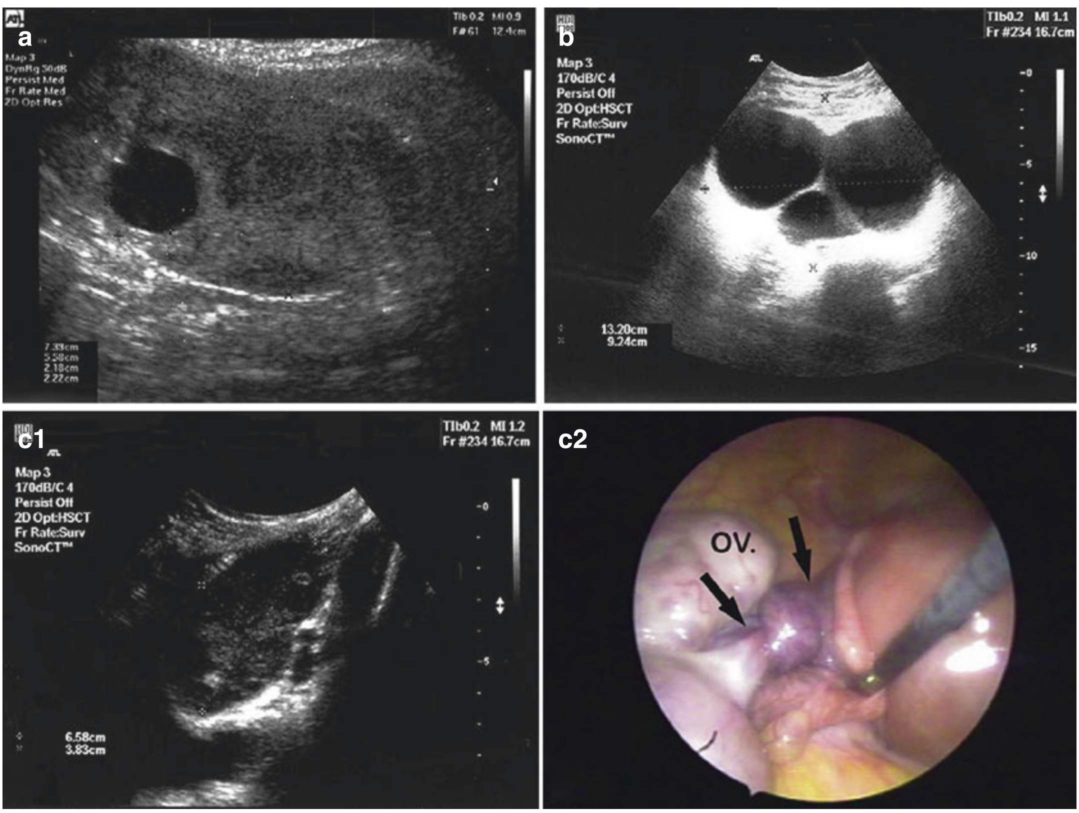

Fig. 12.2 Different ultrasound images of twisted ovaries in pregnancy. (**a**) A transabdominal scan of an enlarged ovary with a 20 mm simple unilocular cyst. The ovarian parenchyma appears edematous; (**b**) transabdominal scan of an enlarged 130 × 92 mm ovary with multicystic components; (**c1**) transabdominal scan of an enlarged 65 mm ovary without cystic components. The ovarian parenchyma appears edematous; (**c2**) laparoscopy of the same patient as in (**c1**). *Arrowheads* point to the twisted ovarian pedicle. Reproduced with permission from [43]

solid-appearing ovary, unilateral ovarian enlargement, ovarian peripheral cystic structures, and marked stromal edema and pelvic fluid [54, 71–75].

OHSS presents a significant differential diagnostic problem. Twisted adnexa are usually characterized by a solid-appearing ovary on ultrasound, enlargement of the organ, ovarian peripheral cystic structures, and marked stromal edema and pelvic fluid. These characteristics are routinely present in a hyperstimulated ovary, and usually, both adnexa are enlarged. Mild OHSS could be suspected in these patients, delaying the correct diagnosis and treatment. There is an overlap in the gray-scale appearance of ovaries in mild OHSS and OT. Ovaries in mild OHSS are enlarged, with prominent, heterogeneous stroma and contain multiple 1–2 cm follicles, many containing hemorrhages. Torsed ovaries are also enlarged, with prominent, heterogeneous central stroma and with multiple, small, peripheral follicles [76]. In addition, in OHSS, both ovaries could be enlarged, and symmetry among them may be present contrary to the situation with AT [65].

Although the absence of Doppler flow indicates arterial occlusion and AT (high specificity) (Fig. 12.3), the presence of flow (Fig. 12.4) should not exclude the diagnosis of AT (low sensitivity) [72–75, 77, 78]. This matter depends on the stage of the torsion and the degree of vascular compression. During the early stage of torsion, the venous and lymphatic systems are affected. Arterial flow may only be decreased at this stage. The Doppler sonography correctly diagnoses AT in general female population in 40–60% of surgically confirmed cases [14, 78, 79]. With OHSS, ovaries often show an increase in diastolic blood flow; thus, decreased blood flow may indicate AT in a patient with OHSS [78, 80]. Furthermore, the reduction in diastolic flow is diagnostic of OT in patients with OHSS. In the hyperstimulated ovary, the diastolic flow is usually increased [81]. However, a torsed ovary may demonstrate normal venous and arterial flow completely symmetric to the normal side [76].

Fig. 12.3 Doppler mapping of the left adnexa showing absence of vascular flow. Reproduced with permission from [77]

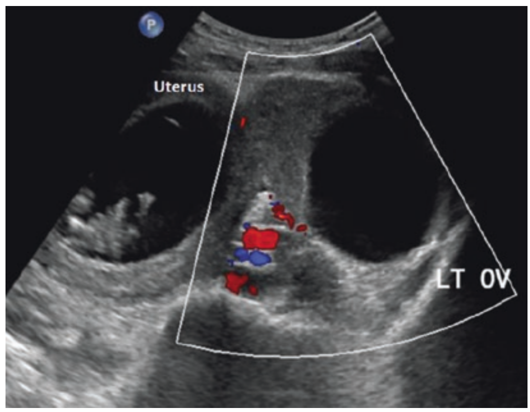

Fig. 12.4 Doppler sonogram showing intrauterine pregnancy and left ovarian cyst with flow to the ovary, intraoperatively found to be ovarian torsion. Reproduced with permission from [68]

> The decision for surgical evaluation should not rely only on the results of Doppler flow investigation and should also take past medical history, clinical appearance, and laboratory assessment into account [14, 65]. Close monitoring is necessary in order to achieve timely management with a conservative approach.

12.7.3 Abdominal CT

Abdominal CT is rarely performed in pregnancy. Most cases underwent CT scan in puerperium [47]. The correct preoperative diagnosis of AT in a general female population based on CT findings is only 34% [82]. The most common but nonspecific finding of OT in a general female population on CT scan is an enlarged ovary (Fig. 12.5) (>4 cm in maximal dimension) with or without a mass [83].

12.7.4 Abdominal MRI

MRI is useful in the diagnosis of OT in 2nd and 3rd trimesters of pregnancy where the ovaries are difficult to visualize by ultrasound [84]. Also, if the diagnosis cannot be established, especially in cases with OHSS, emergent MRI of the abdomen and pelvis could define the AT. The MRI appearance of AT includes hemorrhagic Fallopian tube and a twisted ovarian tumor that can result in hemorrhagic infarction with the lack of enhancement in the multiple internal septa of the tumor [85]. Solid ovarian tissue appears enlarged and edematous (Fig. 12.6).

Currently, the diagnosis of AT is missed in 15–35% because of nonspecific clinical features and uncommon objective findings [7, 44, 86]. Probably more frequent use of MRI in doubtful cases could increase the preoperative diagnostic accuracy.

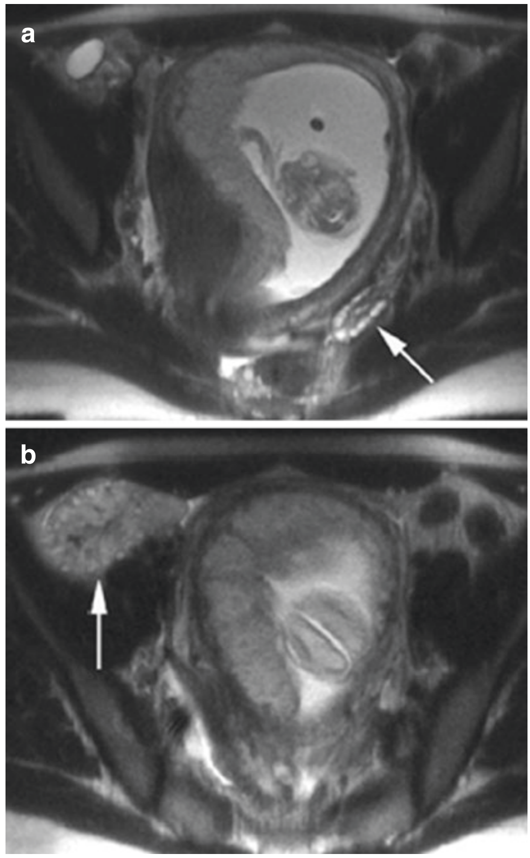

Fig. 12.6 Ovarian torsion at 15 weeks of gestation. (**a**) Transverse image shows the normal left ovary with normal follicles and stroma (*arrow*); (**b**) transverse image shows enlarged and edematous right ovary (*arrow*), which is consistent with torsion [87]

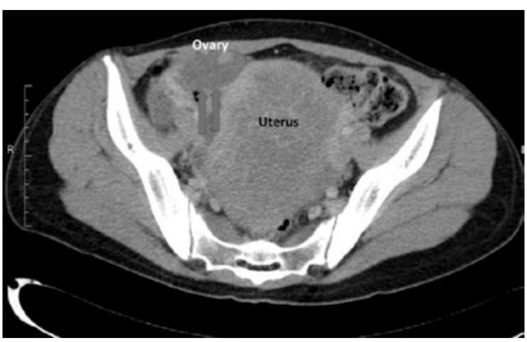

Fig. 12.5 The right ovary was slightly enlarged and located anterior to the uterus (*arrow*). Reproduced with permission from [47]

12.8 Treatment

In emergency settings, early diagnosis is important because prompt surgical intervention can result in ovarian preservation by saving the ovary and adnexa from infarction. In elective settings, because of the high incidence of adverse pregnancy outcomes in association with emergency surgery, some recommend elective removal of all masses that persist until 16 weeks and are 6 cm or greater regardless of appearance on imaging studies, unless it is suspected to be a leiomyoma [88].

12.8.1 Operative Principles

12.8.1.1 Abdominal Access

> *Laparoscopy is recommended for both diagnosis and treatment of adnexal torsion unless clinical severity warrants laparotomy.*
>
> SAGES guideline

Sometimes AT produces no classic symptoms, and there are no definitive diagnostic tests or studies; surgical exploration of the pelvis is required for definitive diagnosis (Fig. 12.7). Traditionally, this was done by laparotomy; however, laparoscopy has become the preferred surgical approach for both diagnosis and management of AT in pregnancy [89]. In an attempt to overcome the potential adverse effects of pneumoperitoneum on the fetus, gasless laparoscopic surgery (GLS) has been developed. GLS in pregnancy has comparable outcomes to conventional CO_2 laparoscopy, but it is associated with some advantages. Hypercarbia and increased intraperitoneal pressure due to CO_2 insufflation are avoided. Literature search up to 2013 found two case reports of GLS-treated AT during pregnancy. Both performed successful GLS operation using the Laparofan (Origin, Menlo Park, CA) [90, 91].

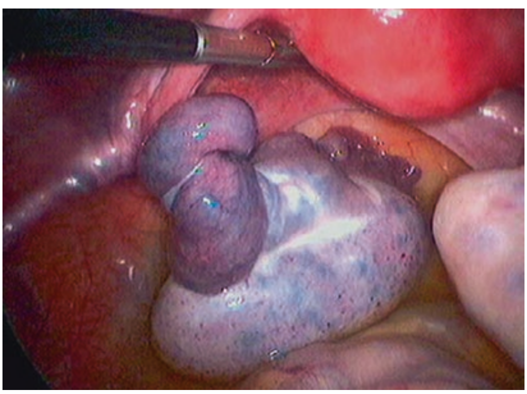

Fig. 12.7 Laparoscopic view of torsion of the enlarged left adnexa. Reproduced with permission from [56]

12.8.1.2 Adnexal Preservation or Resection

Traditionally, AT was treated aggressively with salpingo-oophorectomy of the involved side; unwinding the torsion was condemned for fear of releasing a potentially fatal embolus [92, 93]. This was not confirmed, and current conservative operative management involves unwinding the adnexa and assessing its viability. No emboli in the general population have been noted using this approach [22, 94]. Once torsion is unwound, the adnexa show one of the following:

- No evidence of ischemia or mild ischemia with immediate and complete recovery (Fig. 12.7)
- Severe ischemia with a dark red or black tube and the ovary and partial recovery after the pedicle is untwisted (Fig. 12.8)
- Gangrenous adnexa without recovery (>48 h)

Only the gangrenous adnexa need complete removal; the first two situations can be conservatively treated with detorsion and preservation of the ovary, even after severe ischemia has occurred [22].

> When a (para)ovarian cyst is present, a complete ovarian cystectomy should be performed to obtain a histological diagnosis [94] and to prevent recurrence. Untwisting of the pedicle of the cyst should be avoided to prevent emboli and toxic substances related to hypoxia from entering peripheral circulation.

Routine ovariopexy after detorsion does not seem warranted because the risk of retorsion is very low when a cause is found and treated [94]. Despite the necrotic, hemorrhagic, or bluish-black appearance of a torsed ovary, detorsion saves over 90% of these ovaries, and ovarian function recovers [20, 22, 23, 74, 95]. Even with complete ischemia, gross appearance does not correlate with the outcome and that detorsion within 24 h did not show an increase in free radical reperfusion injury [96]. The importance of

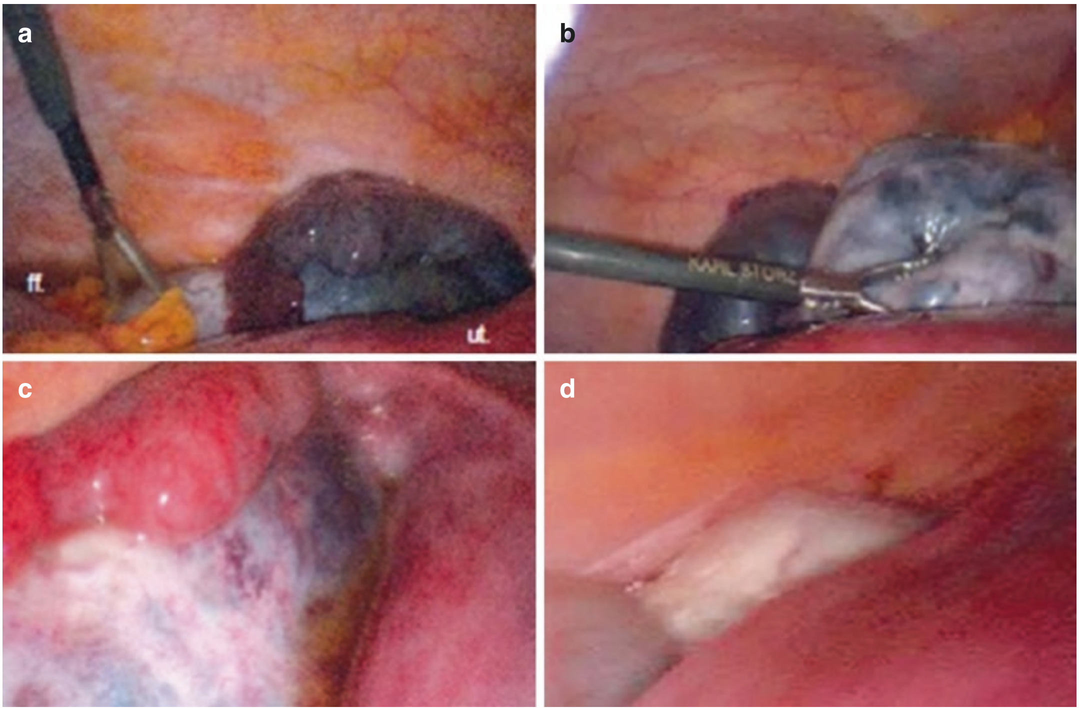

Fig. 12.8 (**a**) Torsioned right ovary; (**b**) detorsion of ovary; (**c**) 3 min after detorsion; (**d**) normal left ovary. *ut* uterus, *ff* free fluid. Reproduced with permission from [51]

early diagnosis and surgical intervention in the case of AT is highlighted by a report showing that the delay of intervention for 36 h resulted in significant congestion and necrosis [96]. Assessment of ovarian viability such as ultrasound visualization of follicular development, inspection during a subsequent procedure, observed response to stimulation during IVF, and documentation of fertilization of oocytes from the ovary has consistently shown that the ovary does recoup function after torsion and detorsion [20, 22, 23, 25, 95]. Furthermore, because an increased risk of thromboembolism has not been associated with detorsion procedures [20, 23], conservative management with detorsion is encouraged. In general female population, an overall morbidity with salpingo-oophorectomy (12%) was significantly higher than in the conservatively treated control group (3%) [97]. Adnexectomy can be avoided in all cases and therefore fertility preserved [56]. After unwinding, aspiration of ovarian cysts, if present, is recommended [77].

Since the successful conservative management of AT in general female population was described by Mage et al. in 1989 (laparoscopically) [94] and Bider et al. in pregnant population in 1991 [44], this technique has been extended to the management of such conditions during pregnancy. Laparoscopic detorsion of AT is recommended as the first-line treatment. It is successfully performed during pregnancy up to 20 weeks of gestation, first performed laparoscopically by Levy et al. in 1995 [98]. Around 60% of patients treated with laparoscopy in pregnancy with most of the cases in the first trimester (75%) [86] but even in the early third trimester can be performed [77]. The patients who underwent laparoscopy had a significantly smaller ovarian mass and a shorter hospital stay. Compared with laparotomy, laparoscopic procedures are associated with shorter hospitalizations, a lower rate of febrile morbidity, reduced consumption of narcotics, and greater patient comfort [20, 23]. After laparoscopic detorsion, 24 h of postoperative observa-

tion is recommended [99, 100]. The incidence of operative procedures is detorsion followed by cystectomy in 80%, oophorectomy in 10% for masses larger than 12 cm, and simple detorsion in 10% [86]. Smorgick et al. [43] performed detorsion in all their cases in their series of 33 pregnant women with OT, followed by cystectomy 12% (4/33) and oophorectomy in one case with a 10 cm cystic teratoma. Of 20 patients who had OT in pregnancy in Bider et al.'s series [44], 85% received detorsion, followed by biopsy, aspiration, and cystectomy in 45% patients. In Hasson et al.'s study [14], all patients received detorsion and 55% also undergoing an additional procedure(s).

12.8.1.3 Underlying or Concomitant Disease

Special attentions should be placed on AT in patients with OHSS. First, due to other symptoms and signs of OHSS that can mask AT, the diagnosis is delayed making the prognosis of AT worse. Second, moderate or severe OHSS can present with symptoms and signs of increased intra-abdominal pressure or even abdominal compartment syndrome (see Chap. 22).

There are cases of AT with concomitant other emergent abdominal condition, such as contralateral tubal ectopic pregnancy (Fig. 12.9) [101, 102] or acute appendicitis [58]. In cases with contralateral tubal ectopic pregnancy, it is especially important to make early diagnosis and laparoscopic exploration to save the detorsed adnexa because salpingectomy or adnexectomy is commonly indicated in the contralateral adnexa due to ectopic pregnancy. Such procedure preserves fertility.

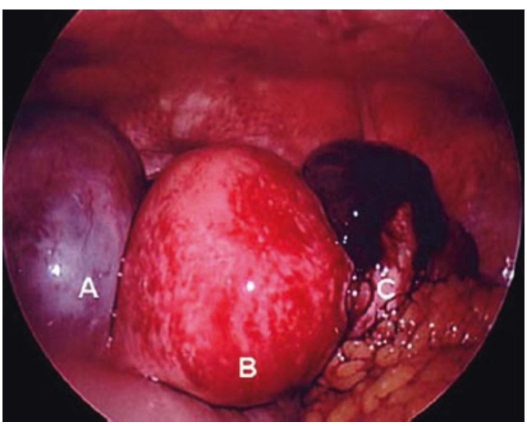

Fig. 12.9 (**A**) Adnexal torsion and concomitant contralateral ectopic pregnancy (**C**); (**B**) uterus. Reproduced with permission from [102]

12.8.2 Operative Techniques

12.8.2.1 Detorsion/Unwinding

Laparoscopy

A small incision of 2 cm is made in the left upper abdominal quadrant (Fig. 12.10) and a 10 mm trocar is introduced as open (Hasson) technique on the left side of the epigastrium. Pneumoperitoneum is induced with an insufflation volume of CO_2 of 1 L/min and an intra-abdominal pressure of 10 mm Hg. The patient is kept in a horizontal

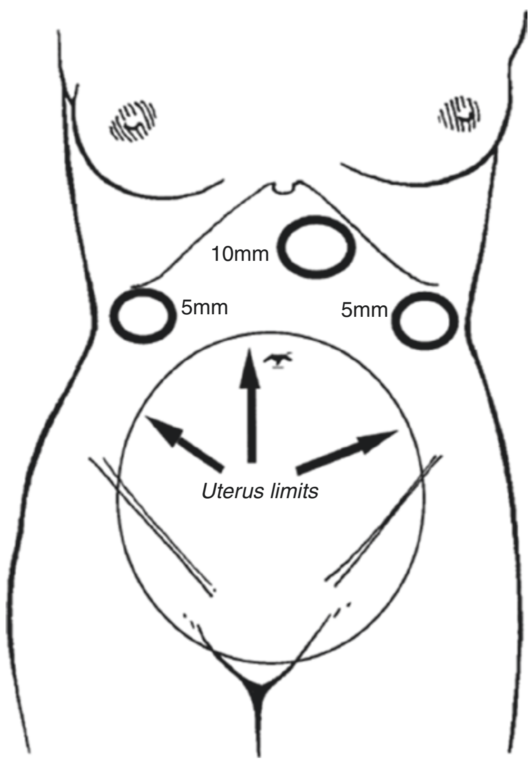

Fig. 12.10 Sites of trocar insertion in the third trimester of pregnancy for laparoscopic detorsion of adnexal torsion (*circle* marking upper limits of the uterus). Reproduced with permission from [77]

position. Secondary trocars are inserted at opposite sites, one in the right upper abdominal quadrant and the other on the extreme left of the middle abdominal quadrant. These secondary trocars are inserted under direct laparoscopic control. Two atraumatic probes are introduced into these trocars: one on the left side, allowing washing and gentle pressure on the uterus in a brief lateral Trendelenburg position and with the other probe elevating the twisted adnexa, pushing it contralaterally to the direction of rotation. The aid of two probes without grasping the tissue avoids bleeding. Serial manipulations achieve the unwinding of the adnexa. The release of pressure ensures the normal positioning of the adnexa. The lateral Trendelenburg position is then abandoned, and after abundant washing, the procedure is stopped for 10 min, with disinflation of the abdominal cavity. Once the procedure resumed, the pedicle of the ovary and the tube is carefully examined, and an improvement in color and a decrease in edema should be noted. These signs establish the beginning of the recovery of the adnexa, which should turn pink shortly after the procedure. Aspiration of ovarian cysts, if present, is recommended. However, this is not always possible since cysts are often filled with clotted blood.

Cardiotocography should be carried out during the entire procedure [77].

Single-Incision Laparoscopic Surgery

Recently, AT was treated by single-incision laparoscopic surgery (SILS, LESS, SSA) [103, 104]. An advantage of SILS is that it is, by a definition, a laparoscopy with open access, minimizing the possibility of intra-abdominal injury. It is especially suitable for the pregnancies up to 20 weeks when the uterus is below the umbilicus (Fig. 12.11a). A single port is introduced through a 2–3 cm vertical umbilical incision to the peritoneal cavity (Fig. 12.11b). Layer by layer, the peritoneal cavity is entered; then 0 polyglactin 910 sutures are placed at each side of the fascia (as stay sutures to help in final closure at the end of the procedure). The SILS device is inserted into the transumbilical wound opening. The cyst with or without the adnexa can be resected intra- or extracorporeally (Fig. 12.11c) [103].

The SILS advantages include better cosmesis because of a hidden umbilical scar and the need for fewer trocar incisions, a possible decrease in morbidity related to the visceral and vascular injuries during trocar placement, reduced risk of postoperative wound infections and hernia formation, and elimination of multiple trocar site closures. Another potential merit of SILS is the reduction of postoperative pain and narcotic use.

12.8.2.2 Ovariopexy (Oophoropexy)

Performing oophoropexy to eliminate retorsion is controversial in cases where flows return to normal. Although some studies advocate oophoropexy to prevent recurrence, there is not a consensus on this issue.

Oophoropexy in general female population, to prevent recurrence in a form of “triplication” of utero-ovarian ligament, was described by Germain et al. in 1996 [105], where the ligament is plicated and shortened with a running stitch; ovariopexy, where the ovary is sutured to the posterior aspect of the uterus or to the lateral pelvic wall; and oophoropexy, where the utero-ovarian ligament is sutured either to the posterior aspect of the uterus or to the lateral pelvic wall (Fig. 12.12). Oophoropexy, although not evaluated in randomized trials, has been done in women of all ages as well as during pregnancy. Although not commonly done, oophoropexy has been performed laparoscopically with good results and has been recommended for childhood torsion and in women who have previously undergone an oophorectomy for prior OT [9, 105–108]. Although oophoropexy has been performed successfully in pregnant women, it was felt that the increased vascularity of the area precluded performing this procedure. Owing to the concern of yet another recurrence, and the length of the utero-ovarian ligament, the ligament is shortened. In this approach, a grasping forceps is passed through an endoloop and then used to tent up the utero-ovarian ligament in the midsection. The pre-tied endoscopic knot is then tightened, pulling the ovary close to the uterus and shortening the utero-ovarian ligament [33].

In a review from 2004, 78 cases of AT during pregnancy were reported. The operative access

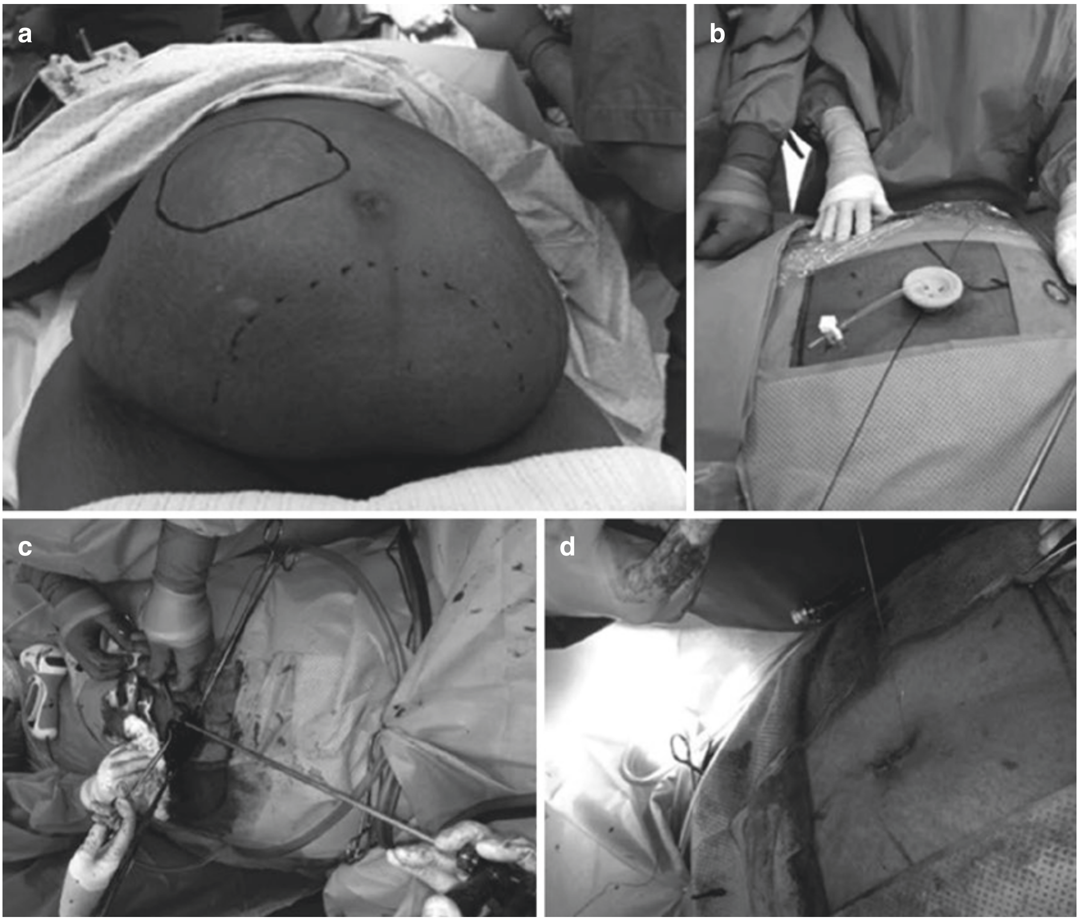

Fig. 12.11 (**a**) The site of the twisted ovarian mass at right upper quadrant (*circle*) and the pregnant uterus location (*dotted line*); (**b**) view of the transumbilical SILS device insertion; (**c**) ovarian cystectomy using exteriorization method; (**d**) view of closing the skin incision. Reproduced with permission from [103]

was laparoscopy in 74% and laparotomy in 18%. Sixty-two percent were treated by preserving the ovary. This included unwinding the adnexa, with or without cystectomy. In 38%, an oophorectomy or adnexectomy was performed. An oophoropexy was done in two cases [108].

12.8.2.3 Laparotomy

If the preoperative diagnosis is more or less known, classic Pfannenstiel incision is used [68]. When the diagnosis is uncertain or significant bleeding expected, low midline incision is recommended. When acute appendicitis is suspected, McBurney's gridiron incision is used which suffices for the operations on right adnexa [45].

In the presence of an ovarian cyst, a simple cystectomy can be performed in the absence of overt malignancy. When possible, the entire ovary is delivered from the abdominal cavity and surrounded by moist laparotomy pads to avoid intra-abdominal spillage of cyst contents if rupture occurs. The thin ovarian capsule is carefully incised, usually with a scalpel. Blunt dissection is used to separate the cyst from the ovarian tissue. Electrosurgery can be used on the internal ovarian surfaces for hemostasis but should not be used near the cyst wall to minimize the risk of cyst rupture [109].

Rupture is inevitable in some ovarian cysts, particularly in endometriomas and functional cysts, such as luteomas. If a dermoid is acci-

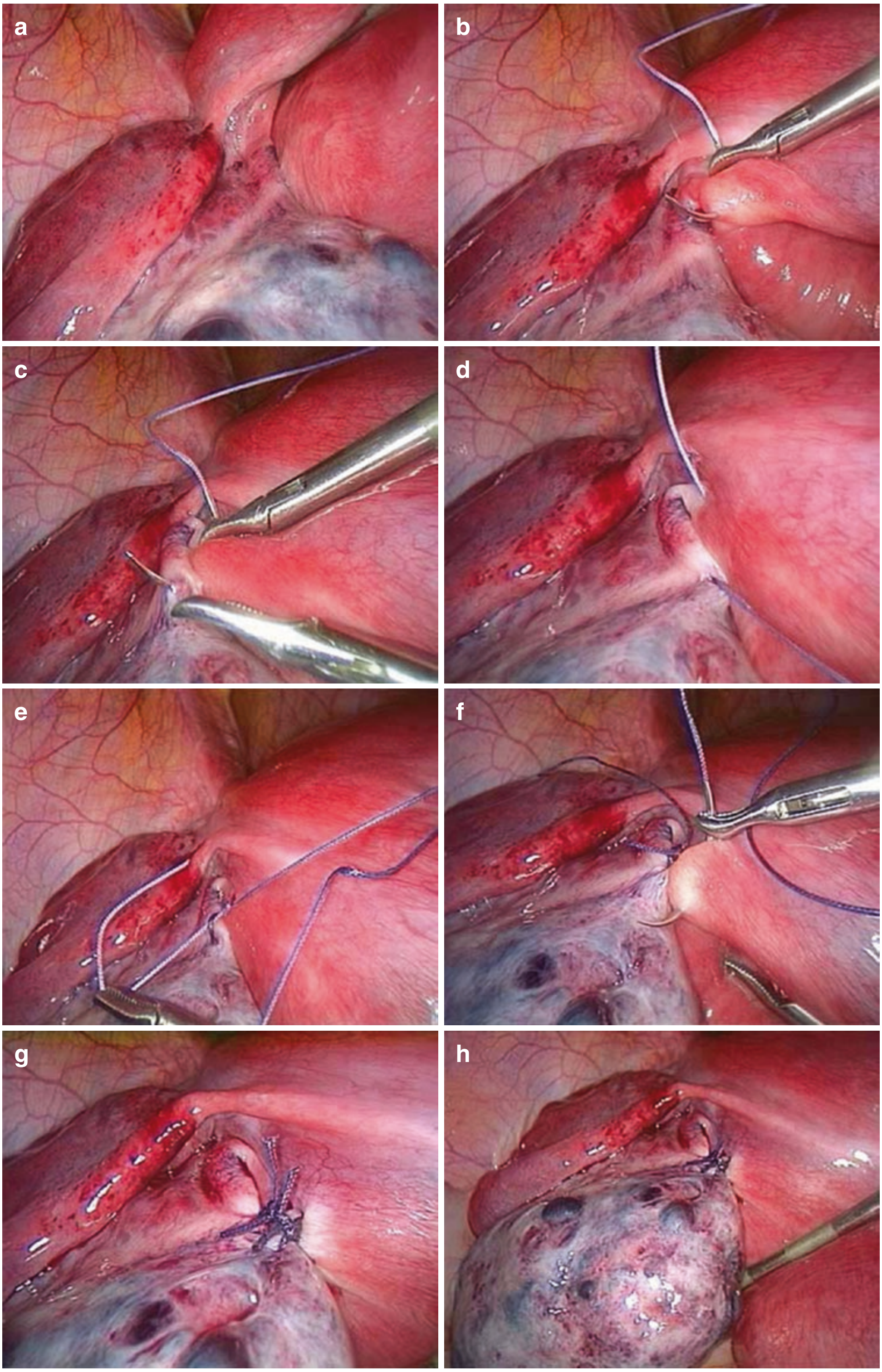

Fig. 12.12 Oophoropexy of the recurrent torsion of the left ovary at 15 weeks of gestation. (**a**) Intraoperative finding after ovarian detorsion; (**b**–**e**) shortening of the proper ovarian ligament by suturing the distal and proximal end of the ligament for prevention of recurrent ovarian torsion in pregnancy; (**f**–**h**) ovarian fixation for the remaining proper ovarian ligament. Reproduced with permission from [108]

dentally ruptured, every effort should be made to avoid spilling the very irritating sebaceous contents into the peritoneal cavity. If this occurs, prolonged peritoneal irrigation with warmed saline will prevent peritonitis. Likewise, if the “chocolate” contents of an endometrioma or the fluid content of a potentially malignant cyst spills within the peritoneal cavity, prolonged irrigation with warmed saline is judicious. It remains to be determined if these precautions avoid the detrimental effect of intraoperative rupture on stage I ovarian cancer [110].

Regardless of rupture, all cysts should be completely opened after removal and the internal surface of the cyst wall examined for excrescences. When present, microscopic examination of frozen sections can help determine if intraoperative staging is required. In all cases, definitive diagnosis must await careful examination of permanent sections.

The ovary does not require precise reconstruction as was thought in the past. Reapproximation with internal sutures may help subsequent reformation of the normal ovarian profile, but sutures on the external ovarian surface should be avoided to minimize the subsequent risk of adhesion formation [111].

12.8.3 Adnexal Pathology

It is important to define the pathologic cause of the AT. Table 12.2 shows pathology of adnexal masses causing torsion in pregnancy. If the mass is benign, there is no need for additional surgical or oncologic therapy.

Table 12.2 Pathological findings of ovarian torsion in pregnant women. Reproduced with permission from [86]

Pathological finding[a]	(%)
Teratoma	30
Corpus Luteum cyst	20
Follicular cyst	15
Serous cystadenoma	15
Endometrioma	10
Mucinous cystadenoma	5

[a]Two cases undergoing detorsion were without pathological results

12.8.4 Anesthetic and Perioperative Management

See Chap. 21.

12.8.5 Obstetric Management

12.8.5.1 Prevention and Treatment of Preterm Labor

See Chap. 23.

12.8.5.2 Hormonal Pregnancy Support

If the ovariectomy is performed during the first trimester, the patient should receive 17 alpha hydroxyprogesterone caproate 250 mg intramuscularly weekly during 4 weeks as progestogen support for the pregnancy [68]. After this period, progesterone is produced by the placenta. Nevertheless, the persistence of pregnancy is possible even after an early lutectomy [13, 112].

Relaxin mediates lengthening of the pubic ligament, cervical softening, vaginal relaxation, and inhibition of myometrial contractions. Relaxin in plasma of pregnant women is believed to originate exclusively from corpus luteum. Plasma levels peak at approximately 1 ng/mL between 8 and 12 weeks of gestation. Thereafter, they decline to lower levels that persist until term. Relaxin inhibits contractions of nonpregnant myometrial strips, but not those of uterine tissue taken from pregnant women. It also affects cervical remodeling through cell proliferation and modulation of extracellular matrix components such as collagen and hyaluronan [113, 114]. There are no studies about the influence of relaxin after ovariectomy during pregnancy.

12.8.5.3 Ovarian Function

Follow-up ultrasound scans and Doppler studies after detorsion should be performed to show the flow to the ovary and developing follicles which indicate normal functioning ovary. This is important for subsequent pregnancies [68]. First follow-up Doppler scan should be made on the first postoperative day. If the flow is restored and normal, the patient can be safely discharged.

12.9 Prognosis

> A reduced fertilization rate had been attributed to reduced flow in the ovarian artery after ovarian detorsion.

12.9.1 Duration of Symptoms

The time between admission to hospital and surgery is 6–15.5 h and may be significantly shorter in the first trimester. However, several days may pass between the start of symptoms and surgery [25, 43, 56]. In the laparoscopic era, acute symptoms or persistence of complaint mean early surgery (less than 24 h), and treatment is still in time to preserve fertility [56]. Patients in the second and third trimesters are operated significantly later than those in the first trimester. This difference may be either due to a difficulty in assessing the ovaries on palpation and during ultrasound examination or because patients with suspected OT are more readily operated in early pregnancy when the risk from the (laparoscopic) surgery itself is minimal [43]. In one large study, 50% of patients had surgery within 24 h, and 85% received surgery within 72 h [86].

A reduced fertilization rate of 40% for oocytes aspirated from a detorsed ovary is significant, compared to 93% from the unaffected ovary. Seventy-five percent of oocytes from the unaffected side and 64% of oocytes from the affected side developed into blastocysts [115]. In a repeat IVF procedure, retrieved oocytes from laparoscopically detorsed ovaries could be subsequently fertilized. Therefore detorsion is recommended as the procedure of choice for ischemic ovaries [23]. The subsequent course of pregnancy after treatment for AT is generally favorable; abortion rates of 8.3–16.6% do not appear to be increased [14, 25], with 60% of pregnancies continued to term with the vaginal delivery of healthy children [56]. In one large study, there were 60% term deliveries, 15% preterm deliveries (third trimester), 5% missed abortions, and 20% elective abortions in the first trimester. There was no significant difference in pregnancy results between laparoscopy and laparotomy. CS for common obstetric indications was indicated in 27%, and 73% underwent vaginal deliveries [86]. Delivery at the term of healthy babies occurs in 61–83% of patients [14, 43, 44].

12.9.2 Risk of Recurrence

Laparoscopic fixation of the adnexa (ovariopexy) or shortening of the utero-ovarian ligament can be done to avoid recurrence of AT, but this should be the exception rather than the rule [32, 33, 106, 108]. Reported recurrence rate is 19.5% for pregnant women and 9.1% for nonpregnant women; however, 73.2% of pregnant women and 20.8% of nonpregnant women had been treated with ART before torsion [14]. There was no recurrence in a study with five patients during the subsequent course of the pregnancy [56]. Torsion recurrence is higher in patients with OHSS [32, 116].

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Isolated Fallopian Tube Torsion

13

Abstract

Isolated Fallopian tube torsion is an extremely rare condition in pregnancy. There are less than 50 cases published. Risk factors include mechanical, anatomical, physiological, and pathologic conditions. Specificity of this condition is that more than 90% develop on the right side. Clinical presentation is the same as for adnexal torsion, and sometimes even with abdominal ultrasound, the preoperative distinction between adnexal and Fallopian tube torsion is not possible. Differential diagnosis is wide, as for adnexal torsion. As the condition appears predominantly on the right side, it is commonly misdiagnosed as an acute appendicitis. Suspicion of Fallopian tube torsion is an indication for operative intervention. Laparoscopy is the abdominal entry of choice. Detorsion is the procedure of choice even when ischemic changes are present. If vitality is not restored after detorsion, resection is indicated.

13.1 Historical Perspective

The first description of isolated Fallopian tube torsion (IFTT) in adults was in 1890 by Bland-Sutton [1]. It was caused by hydrosalpinx three and a half times twisted and removed by Henry Morris. The specimen is preserved in the Museum of Royal College of Surgeons. One of the first reviews on the subject was by Hamilton Bell in 1904 [2]. The first pediatric case was reported by Hansen in 1922 [3]. First known description of two cases during pregnancy was by Praeger in 1899 [4], then Pozzi in 1900, and two cases by Pinard in 1901–1902. McKerrow in 1934 [5] and later Savage (Department of Obstetrics, School of Medicine, University of Maryland Baltimore, Maryland, USA) in 1936 [6] collected 13 previously published cases and added one of his own.

13.2 Incidence

Torsion of hydatids of Morgagni involving the ipsilateral Fallopian tube has been advocated as a cause of acute abdominal pain in adolescents, being involved in about 25% of adnexal torsions in this subgroup. However, the condition is uncommon in the adults, representing a marginal part of adnexal torsions [7–10]. The incidence of IFTT from previous reports was 1/1,500,000 [7, 11]; however, the incidence appears to be higher. West Hertfordshire NHS Trust claimed 1/125,000 in the period of 3 years. IFTT in pregnancy involves 12–20% of cases [12–14], some claiming an incidence of 1/120,000 from a 10 year period (1991–2000) [13]. Available literature from 1900 revealed 23 publications

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_13

reporting 29 cases [6, 9, 13, 15–44]. The distribution across trimesters was [7]:

- First trimester: 13.3%
- Second trimester: 20%
- Third trimester: 60%
- Intrapartum: 6.7%

13.3 Risk Factors and Pathophysiology

13.3.1 Risk Factors

It is a fact that the Fallopian tube, when distended with simple fluid and blood, pus or even when gravid, does twist its pedicle.

Sir John Bland-Sutton, 1904

IFTT in general female population can occur at any age, and most of the patients are under 30 years of age. Factors that possibly influence the occurrence of IFTT could be divided into two categories: *intrinsic factors* such as congenital anomalies of the Fallopian tube and acquired pathology of the Fallopian tube, for example, hydrosalpinx, hematosalpinx, neoplasm, surgery, autonomic dysfunction, and abnormal peristalsis, and *extrinsic factors*, for example, changes in the neighboring organs such as neoplasm, adhesions, pregnancy, mechanical factors, movement or trauma to the pelvic organs, or pelvic congestion [45]. Broader classification of causes and theories for IFTT in general and pregnant population can be presented as [7–9, 13, 14, 34, 36, 39, 40]:

- *Anatomic abnormalities*: long mesosalpinx, tubal abnormalities, hematosalpinx, hydrosalpinx, varicose veins in mesosalpinx, hydatid of Morgagni, tubal ectopic pregnancy, paratubal cyst
- *Physiological abnormalities*: abnormal peristalsis or hypermotility of the tube (autonomic dysfunction), tubal spasm, and intestinal peristalsis
- *Hemodynamic/hormonal abnormalities*: venous congestion in the mesosalpinx (progesterone effects of edema and increased tissue vascularity)
- *Sellheim theory*: sudden body position changes
- *Trauma, previous surgery, or disease*: tubal ligation, PID, tubal endometrioma
- *Gravid uterus*: direct mechanical cause and progesterone effects of edema and increased tissue vascularity
- *Normal Fallopian tube*

13.3.2 Pathophysiology

The mechanism underlying IFTT in both general and pregnant population is apparently a sequential mechanical event. The process begins with the mechanical blockage of the adnexal veins and lymphatic vessels by an ovarian tumor, pregnancy, hydrosalpinx, or pelvic adhesions after tubal infection or pelvic operation. This obstruction causes pelvic congestion and local edema with subsequent enlargement of the Fallopian tube, which in turn induces partial or complete torsion [46]. Torsion pronounces venous stasis and subsequent edema. Hypoperfusion determines tissue hypoxic ischemia and whether the degree of twisting is severe enough to exceed arterial blood pressure. The late step is complete blood stasis and ischemic necrosis. At this stage, cellular damage is usually irreversible, and reperfusion determined by the untwisting is not followed by restitutio ad integrum. A torted Fallopian tube undergoing necrosis has potential to cause serious infection similar to that of a perforated appendicitis [47]. There is even a case of the Fallopian tube accompanied by a paratubal cyst coiling tightly 2.5 times around the ovary, causing congestion and enlargement of the ovary [48].

IFTT in pregnancy is more common on the right side with incidence of 90% [7–9, 14, 17, 21, 22, 24, 27, 28, 30, 31, 35–37, 39–43, 48], while only 10% are on the left side [13, 16, 23, 29, 33, 34]. Possible explanations are:

- The left-sided Fallopian tube has less mobility due to its proximity to the sigmoid mesentery [9, 36, 40]

- Slow venous flow on the right side, which may result in congestion.
- Hypermobility of the cecum and ileum [9].
- Cases of right-sided pain are commonly operated because of the suspicion of acute appendicitis [8, 36], whereas left-sided cases may be missed and resolve spontaneously

13.4 Clinical Presentation

The most common presenting symptom is a pain, which begins in the affected unilateral lower abdomen or pelvis (typically at the level of the right uterine angle) and may radiate to the flank or thigh [8, 9, 14, 31, 32, 36, 39, 40]. The onset of pain is sudden and cramp like. Most commonly the pain is constant but may be intermittent if partial or total detorsion occurs [21, 32, 36, 40]. Pain duration is usually less than 48 h but can last up to 10 days [35]. During labor, the pain unrelated to uterine contractions is present [7], or persistent pain is present after (induction of) labor [27]. Other associated symptoms include nausea, vomiting, and bowel and bladder complaints, such as urgency but with no associated dysuria [8, 9, 13, 16, 21, 36, 39, 40]. Some patient can recall previous episodes of similar symptomatology, mostly less intense, indicating recurrent IFTT [41]. Some patients may have the same or similar episodes after operative detorsion [49]. There is no disturbance of bowel action.

Most commonly, physical examination reveals good general condition and afebrile state with stable vital signs [16, 21]. Low-grade fever, present in 15% of patients, indicates necrotic changes of the Fallopian tube [22, 50]. Abdominal tenderness is obtained in almost all of the patients, and guarding can develop in advanced cases [7, 39, 40]. The abdomen shows normal fundal height corresponding to the period of gestation. The uterus is relaxed with a regular fetal heart without uterine contractions. Tenderness is present in the lower abdominal quadrant, on the side where the IFTT occurs. A tender adnexal mass may be palpable. Pelvic examination may reveal palpable tender, tense adnexal mass associated with cervical tenderness [51]. The vaginal examination shows a closed cervix without any evidence of bleeding or any abnormal discharge. If there is scant uterine/vaginal bleeding, it occurs after the onset of the pain and is presumably due to pelvic venous congestion. The bowel sounds are not altered. Varicose veins in the mesosalpinx can rupture and mimic ectopic pregnancy, or concomitant ectopic pregnancy may be present [15], causing massive hemorrhage with symptoms and signs of hemorrhagic shock [52].

13.5 Differential Diagnosis

Because symptoms, signs, and physical findings are associated with other common diseases, the diagnosis of IFTT is rarely established before the operation [7–9, 14, 36, 39, 40, 42, 43]. The correct preoperative diagnosis was present in only 37% of IFTT during pregnancy [50]. The preoperative diagnosis of IFTT of normal-sized Fallopian tubes with normal appearance of the ovaries is extremely difficult. The differential diagnosis is presented in Table 13.1.

13.6 Diagnosis

13.6.1 Laboratory Findings

White blood cell count and erythrocyte sedimentation rate are mostly normal or slightly elevated [9, 16, 21, 36, 39, 40]. If white blood cell count is normal, granulocytosis could be present [16]. High white blood cell count indicates IFTT with necrosis [22]. Urinalysis is commonly normal [16, 21].

Table 13.1 Differential diagnosis of isolated Fallopian tube torsion during pregnancy [8, 9, 21, 35, 36, 40]

Acute appendicitis
Intestinal perforation
Colonic diverticulitis
Ectopic/heterotopic pregnancy
Pelvic inflammatory disease
Twisted ovarian cyst
Ruptured follicular cyst
Degenerating leiomyoma
Placental abruption
Urinary tract disease
Renal colic

13.6.2 Abdominal Ultrasound

Transabdominal and transvaginal ultrasound are mandatory [16, 53]. First, the status of the fetus and the placenta should be checked [16] and then the pathology searched. The ultrasonographic appearance includes an elongated, convoluted cystic mass with good posterior enhancement (Fig. 13.1), tapering as it nears the uterine cornu, and demonstration of the (normal) ipsilateral ovary [53], free fluid, a dilated tube with thickened echogenic walls, and internal debris or a convoluted echogenic mass [54, 55]. The sonographic findings of IFTT are not pathognomonic and are quite variable [23], especially in second and third trimesters of pregnancy, where the adnexa are more difficult to visualize. An IFTT is often misdiagnosed as ovarian torsion. The paraovarian and paratubal cysts are difficult to diagnose when there is the close proximity of a mass to the ipsilateral ovary [56]. In most cases, however, a clear interface is seen between the ovarian surface and the cyst, making diagnosis possible. Sonographic *whirlpool sign* of IFTT is diagnostic [57]. Acute adnexal pain in the presence of a pelvic cystic structure and normal ipsilateral ovary strongly suggests the diagnosis of tubal or paratubal cyst torsion [50]. Varicose veins in the mesosalpinx can rupture and mimic ectopic/heterotopic pregnancy. Transabdominal ultrasound is excellent for ruling out hepatobiliary and urologic pathology.

High impedance, reversal, or absence of reverse end-diastolic vascular flow of the tubal wall can be found on spectral Doppler analysis (Fig. 13.2), but these findings can be difficult to define [56].

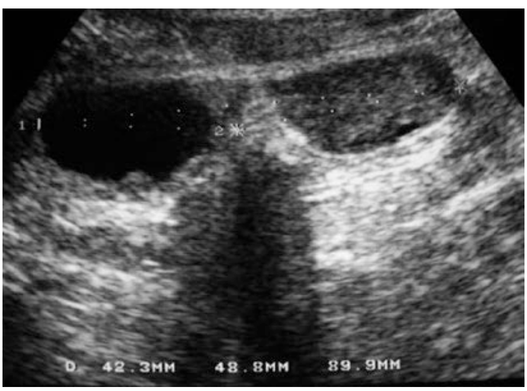

Fig. 13.1 Two ovoid masses with a thin hypoechoic "bridge" between. The superomedial mass is anechoic with a small echoic focus posteriorly, while the inferolaterally situated mass was hypoechoic with uniform low-level echoes within it. They had an appearance of a single bilobed structure with good posterior enhancement. Reproduced with permission from [16]

13.6.3 Abdominal CT

CT findings in general female population (CT is rarely used in pregnancy) with IFTT include an adnexal mass, a twisted appearance to the Fallopian tube, a dilated tube greater than 15 mm, a thickened and enhancing tubal wall, and a luminal CT attenuation greater than 50 Hounsfield units consistent with hemorrhage. Secondary signs of IFTT or adnexal torsion include free intrapelvic fluid, peritubular fat stranding, enhancement and thickening of the broad ligament, and regional ileus [54, 58].

13.6.4 Abdominal MRI

MRI is very accurate for the diagnosis of IFTT in pregnancy and is an excellent alternative to diagnostic exploration [28]. By combining an excellent soft tissue contrast with a large field of view, MRI allows to further differentiate cystic lesions and examine their relationship with intestinal and internal genital structures. T2-weighted MRI findings of dilated and tortuous Fallopian tube in the presence of normal ovary give clue toward the possibility of IFTT [44]. Exclusion of hemorrhage in the dilated Fallopian tube on T1-weighted images additionally confirms the diagnosis of exclusion of tubal ectopic pregnancy (Fig. 13.3). MRI may confirm *whirlpool sign* found on color Doppler ultrasonography, thus helping in making an early preoperative diagnosis [44, 57].

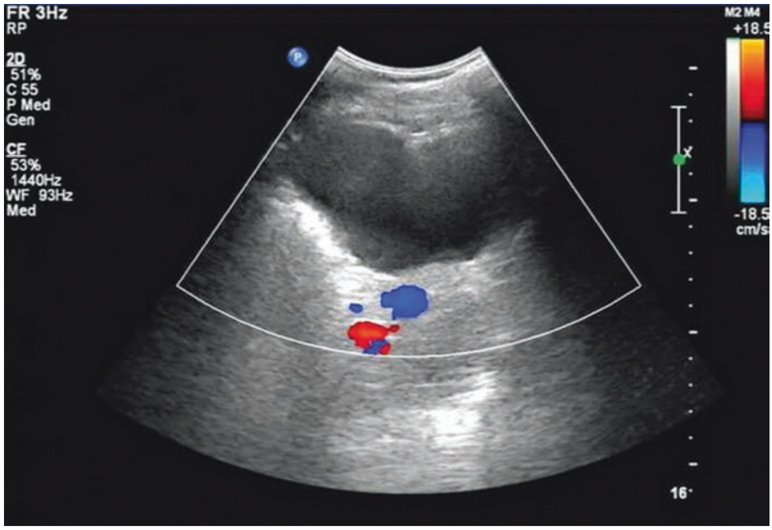

Fig. 13.2 Fallopian tube torsion as an anechoic mass in the right lower abdomen with no vascular flow on Doppler examination. Reproduced with permission from [21]

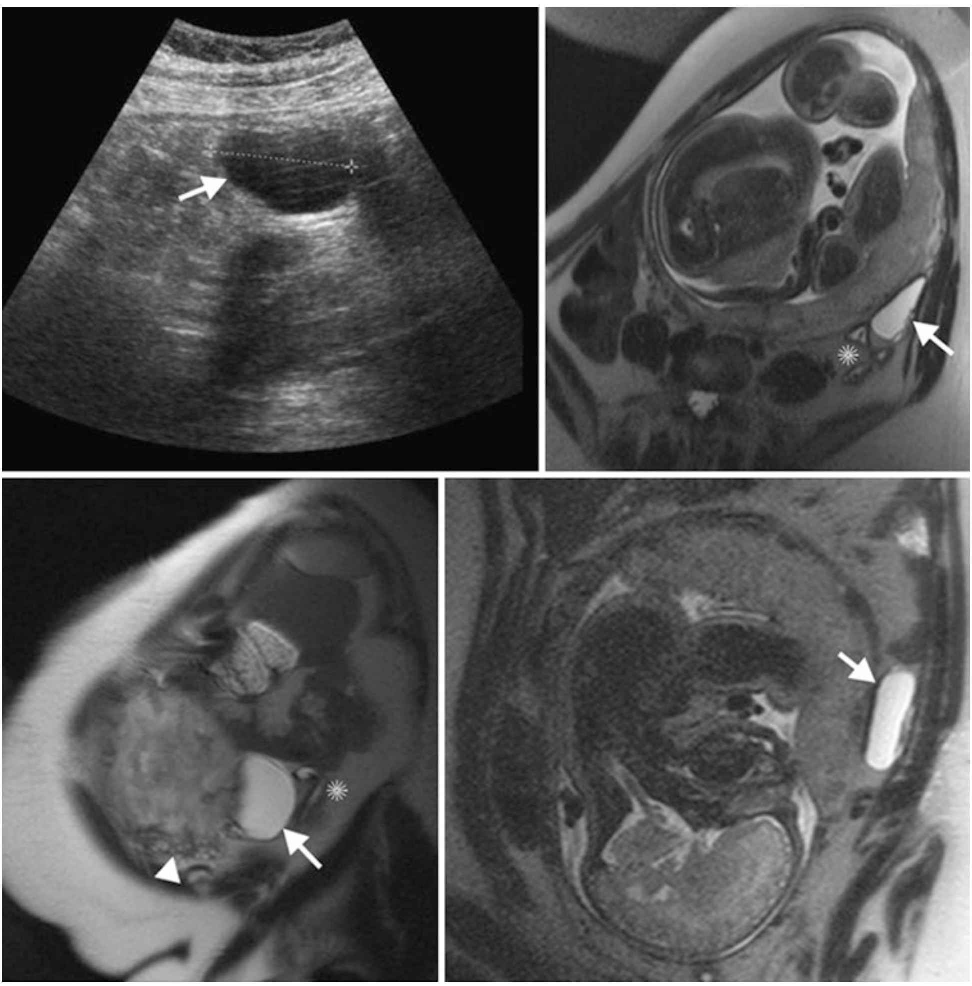

Fig. 13.3 Transabdominal sonographic image (upper left) and T2-weighted MR images (clockwise starting from upper right: axial, coronal, and sagittal view) of the segmental dilation (*white arrow*) of the distal left tube. Note the close pro ximity of the normal-appearing sigmoid colon (*asterisk*) and ipsilateral ovary (*arrowhead*). Reproduced from [44] under the CC BY 4.0

13.7 Treatment

It is important to distinguish between ovarian torsion and IFTT even if both require a surgical approach. The preoperative knowledge of a normal ovarian structure and vascularization by 2D and Doppler flow ultrasound help in the decision of preservation of a normal-looking ovary, as well as when it has been partly damaged due to the adjacent tubal torsion. Thus, it would be possible to preserve the ovarian function while avoiding premature loss of the corpus luteum gravidarum in early pregnancy cases and other adverse obstetric sequelae [36, 42]. Secondly, the preoperative knowledge of a normal ovary could be shared with the patients in order to reduce preoperative anxiety related to eventual oophorectomy. On the other hand, if the patient does not want any more children, some form of operative sterilization could be taken during the emergent operation [35]. Thirdly, reducing unnecessary oophorectomies would probably prevent medicolegal issues when the histology shows a normal ovarian parenchyma.

13.7.1 Abdominal Entry

13.7.1.1 Laparoscopy

Laparotomy is often performed [7, 9, 14, 36, 39, 40, 42], but laparoscopic surgery has steadily increased during the last decades [8, 13] and is recommended as an access of choice in general population [59]. Laparoscopic surgery is safe in the first and second trimester of pregnancy [60], with several cases published even in the third trimester [25, 26, 32]. Advantages of laparoscopic approach are (1) faster recovery, (2) better cosmesis, and (3) fewer pelvic adhesions which are particularly important for women of reproductive age who wish to preserve fertility.

Some precautions should be taken with laparoscopy during pregnancy like pre- and postoperative fetal monitoring, the lateral decubitus position to prevent inferior vena cava compression after 20 weeks of gestation, the Hasson trocar open technique to prevent inadvertent puncture of the uterus (but no studies showed a real advantage over the Veress needle technique), intra-abdominal pressure less than 15 mmHg, and maternal end-tidal volume CO_2 monitored and kept within the normal range; depending on the height of the uterus, the secondary trocars should be inserted under direct vision and their position decided according to the uterus size and the position of the abnormal findings (Fig. 13.4). During the first and second trimesters, trocars can be positioned in standard fashion. In the third trimester, both working trocars should be placed in the right hemiabdomen. First 5-mm trocar is placed in the right middle abdominal quadrant and the second 10 cm above in the midaxillary line [25].

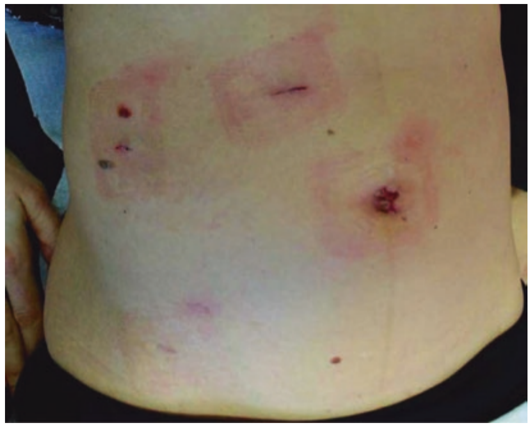

Fig. 13.4 Trocar position for laparoscopic access to twisted Fallopian tube during pregnancy. Reproduced with permission from [28]

13.7.1.2 Laparotomy

Although laparoscopy can be used in the third trimester [25, 26, 32], it is not ideal because of the patient's large uterus which makes it technically very difficult. Therefore, laparotomy is considered the best in the third trimester. Some prefer pararectal incision for direct exposure of the adnexal field, minimizing or eliminating uterine manipulation which is inevitable through inferior median laparotomy [18]. Another benefit of laparotomy is if the patient presents after 32–34 weeks of gestation, Cesarean section can be made, and is advisable, to avoid the influence of possible postoperative complications on the fetus [21].

13.7.2 Surgical Procedures

13.7.2.1 Detorsion (Untwisting)

Indications for untwisting (detorsion) are [7, 9, 14, 15, 36, 40]:

- Twisting is incomplete or recent
- Ischemic damage appears to be reversible
- No malignancy or ectopic pregnancy (suspected)

The presence of ischemic changes while the tube is still twisted does not define vitality (Fig. 13.5a). After untwisting the operator should estimate the vitality of the Fallopian tube (Fig. 13.5b). In some cases the leading pathology, most commonly the tubal cyst, causes IFTT. In these cases, if there is no indication for salpingectomy, the leading pathology should always be resected (Fig. 13.6) to eliminate recurrent torsions [18] and to provide tissue for histologic diagnosis. Excision can be performed by bipolar electrocoagulation or with ultrasonic frictional heating instruments. Excision line should be sutured.

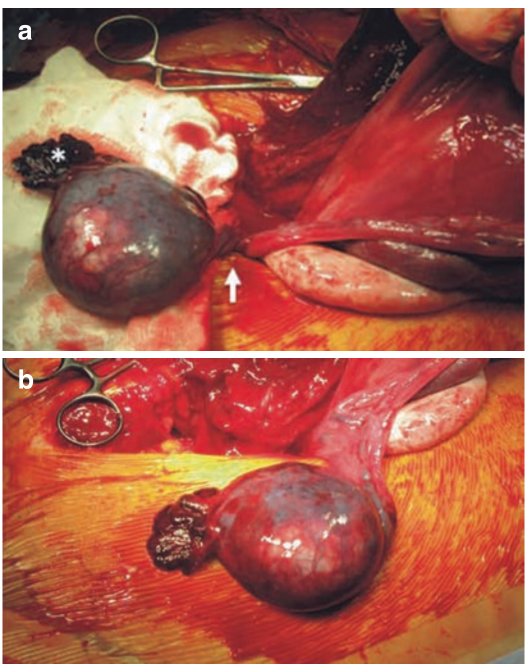

Fig. 13.5 (**a**) An edematous and purple left Fallopian tube showed a threefold torsion around its long axis (*white arrow*). The tubal fimbriae were also purple and enlarged (*asterisk*). (**b**) After detorsion of the vital Fallopian tube, prompt revascularization occurs. Reproduced from [44] under the CC BY 4.0

Untwisting of the pedicle of the cyst should be avoided to prevent emboli and toxic substances related to hypoxia from entering peripheral circulation

If conservation of the affected adnexa is possible, the inferior surface of the tube is sutured to the round ligament by one or two interrupted atraumatic sutures, and the ovarian ligament is shortened by suture to the uterus. Fixation may change the normal anatomy of the pelvis—either moving the adnexa outside from the pelvis or distorting the important close relationship between the ovary and the fimbrial portion of the tube. Branches of both the uterine and the ovarian arteries provide circulation to the Fallopian tube. Shortening of a "billowing" mesosalpinx may impair the blood supply to the adjacent ovary.

Tubal detorsion may help to preserve fertility, but it may also increase ectopic pregnancy risk, especially in recurrent IFTT [49] due to irreversibly distorted Fallopian tube with narrowing or obstruction of the lumen as a consequence of ischemia and/or inflammation (see Sect. 13.3.2).

13.7.2.2 Salpingectomy

There are two indications for total salpingectomy (Fig. 13.7) [16, 22, 31, 35, 41] or partial salpingectomy [21]:

- The tube is beyond recovery (gangrenous, suspected malignancy).
- Distended tube causes other organ impairments, such as ureteric compression

The second indication is not absolute. If during detorsion ureteric flow is normalized, then untwisting (with resection of leading pathology if present) could be performed. Ovaries should always be preserved unless their perfusions are severely deteriorated and necrosis developed. If doubtful, intraoperative biopsy of the Fallopian tube (and ovaries) should be made, increasing the possibility for tubal preservation if histology

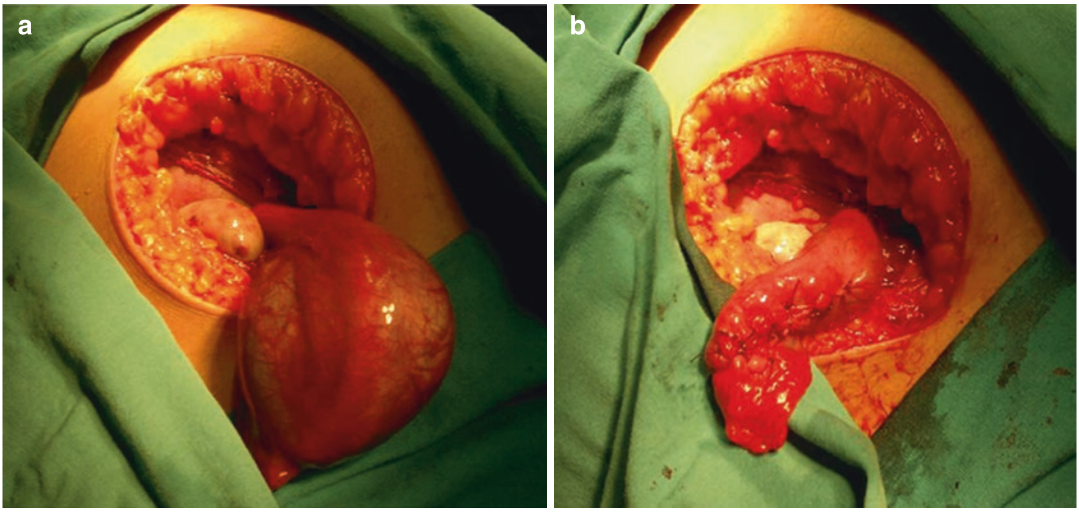

Fig. 13.6 Appearance after (**a**) detorsion of vital Fallopian tube and (**b**) resection of the tubal cyst. Reproduced from [18] under the CC BY Attribution License

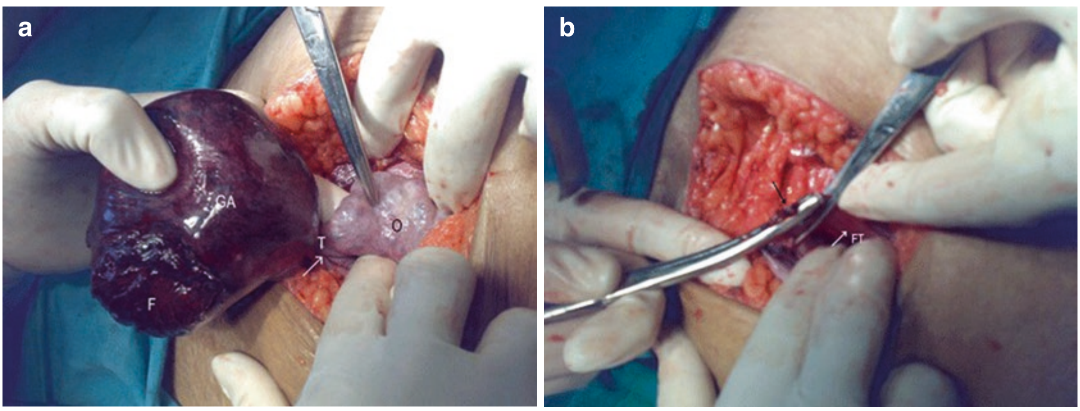

Fig. 13.7 (**a**) 720° left tubal torsion (*T*). (*O*) Normal looking ovary, (*GA*) congested and gangrenous looking tube lateral to the torsion, (*F*) fimbrial end of the tube appearing blocked, leading to hematosalpinx and torsion. (**b**) Site of the resection after salpingectomy (*arrow*) and normal-appearing medial end of the tube (*FT*). Reproduced from [29] under the CC BY 2.5

shows viable tissue. This is important in women without the contralateral Fallopian tube for preserving future fertility.

13.7.3 Anesthetic and Perioperative Management

If the pregnancy is undisturbed, all patients should be monitored clinically and by abdominal ultrasound performed 2 and 4 weeks after discharge [16]. See Chap. 21.

13.7.4 Prevention and Treatment of Preterm Labor

See Chap. 23.

13.8 Prognosis

In the absence of necrosis of the Fallopian tube, fetal and maternal outcome are good. The English language literature concerning twisting or torsion of the Fallopian tube and pregnancy consists of 9

publications reporting 15 cases [13, 15, 16]. There were no associated findings during operation in 26.7% of cases, while reported associated findings were paratubal cyst in 20%, ovarian cyst in 13.3%, and 6.7% of cyst of the mesosalpinx, a cyst in the broad ligament, sactosalpinx, hydrosalpinx, hematosalpinx, and unruptured tubal ectopic pregnancy. Most of the cases were treated with salpingectomy of the affected tube. In all of the cases, the pregnancies ended with a favorable outcome (except tubal ectopic pregnancy). Even the first known description of IFTT in pregnancy from 1899 resulted in the continuation of pregnancy [4].

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14 Complex Ovarian Mass

Abstract

Complex ovarian mass is a separate entity from adnexal torsion which is only one presentation due to ovarian mass and is described in detail in a separate chapter. Complex ovarian mass found in pregnancy is important for several reasons: (1) adnexal torsion, as a result, should be detorsed immediately to preserve ovarian function, (2) persistent pain, (3) ovarian mass rupture and bleeding, and (4) tumor with malignant potential. Persistent pain or compression of surrounding structures is important because it commonly does not subside without surgical intervention. The timing of the operation is critical because intervention during the second trimester carries the lowest risk of obstetric complications. Intra-abdominal bleeding is difficult to diagnose initially, especially if bleeding is small. Bleeding from ovarian mass is always the indication for immediate operation. The most difficult issue is asymptomatic and small ovarian mass. Small ovarian mass can commonly be treated conservatively if the malignancy is excluded. There are different imaging and non-imaging methods for confirmation of malignancy. Malignancy status determines the timing and the type of treatment intervention.

Complex ovarian mass during pregnancy represents not only the mass effect but mass complications during pregnancy. The most common complications include adnexal torsion (see Chap. 12), rupture, bleeding, or obstruction of labor.

14.1 Incidence and Classification

A simple classification of adnexal masses in pregnancy is presented in Table 14.1.

The incidence of histopathologically confirmed ovarian tumors during pregnancy in the largest study up to date is presented in Table 14.2. The most common benign ovarian tumors during pregnancy are cystic teratomas (36–37%), followed by cystadenomas (15–20%) [2–4]. The major concern of an adnexal mass is its potential for malignancy, the incidence of which is usually determined by including ovarian cancers and low malignant potential/borderline tumors. The incidence of malignancy of masses identified during pregnancy is 2–4% [2, 5–8]. There is a trend of low-stage and low-grade cancers, where almost all malignant patients were noted at grade I and stages IA–IC [2, 6, 9, 10].

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_14

Table 14.1 Classification of adnexal masses during pregnancy

Simple	Complex	Solid (benign)	Solid (malignant)
Functional cyst	Endometrioma	Leiomyoma	Sarcoma
Hydrosalpinx	Hemorrhagic cyst	Cystic teratomas	Primary/metastatic
Physiological cyst	Ectopic pregnancy	Fibroma	
		Thecoma	

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Table 14.2 Pathology of benign tumors during pregnancy in decreasing incidence

Type of tumor	Torsion	Elective	Cesarean section	Total
Teratoma	9 (3)	22	45 (9)	76 (37%)
Mucinous cystadenoma	1	14	26 (6)	41 (20%)
Endometrioma	1	8	11	20 (10%)
Corpus luteum cyst	6 (1)	4	8 (5)	18 (9%)
Simple cyst	2	6	2 (1)	10 (5%)
Serous cystadenoma	1	1	7 (4)	9 (5%)
Follicular cyst	1	3	4	8 (4%)
Infarction	7 (3)	0	0	7 (3%)
Paratubal cyst	3 (2)	0	3	6 (2%)
Thecoma/fibroma	0	1	3 (2)	4
Hyperstimulated ovary	1	0	1	2
Cystadenofibroma	1	0	1	2
Brenner tumor	0	0	1	1
Multiple luteinized follicular cyst	0	0	1 (1)	1
Struma ovarii	0	1	0	1
Total	33 (9)	60	113 (28)	206

Reproduced with permission from [2]. Parentheses indicate number of patients with adnexal tumor undiagnosed before surgery

14.1.1 Ovarian Cysts

The number of women diagnosed with ovarian cysts during pregnancy has increased in recent years mainly due to the widespread use of ultrasound in the first trimester. Adnexal cysts can be seen on ultrasound scan in 4.1–24.9% of pregnant women [11, 12]. Around 92% of ovarian masses are simple, unilocular cysts, and of these, 81.6% are less than 3 cm in diameter.

Follicular and corpus luteum cysts of the ovary are functional cysts and benign growths of the ovary. A follicular cyst arises from a normal follicle that fails to undergo ovulation or does not undergo the normal atretic process. It is usually clear and fluid filled. Corpus luteum cysts are less common than follicular cysts but are more associated with clinical symptoms. Ovarian cysts are not commonly found in pregnancy. Eiss, in 1930, reports a case of bilateral tumors, each of which ruptured in pregnancy. Their frequency varies with reports of different series. In Sloane Hospital (1931), the incidence was 1/500 pregnancies; in the University of California Hospital, 1/1500 pregnancies; and in McKerron's compilations (1903), 1/2500 pregnancies [13]. The tumors are thought to occur more often in nonpregnant women of the same relative age for which reason some believe they interfere with conception. Most of the cysts are small; they may or may not grow rapidly during pregnancy. In the first trimester of pregnancy, ovarian cysts are often functional and generally resolve without complications, and therefore these were assumed to be physiological in nature [14–16]. These resolving cysts were classified as cystic or hemorrhagic corpus luteum based on their appearance on gray-scale ultrasound [16].

> The presence of an uncomplicated ovarian cyst is compatible with normal pregnancy, labor, or puerperium [14]

After 16 weeks of gestation, the prevalence of ovarian cysts is 0.5–3.0% [15, 16]. Interestingly,

of the ovarian cysts that persisted at 20 weeks of gestation, 78.6% were present at the 6-week postnatal scan, and all of these were pathological [16]. Zanetta et al. in a recent cross-sectional study assessed the prevalence of ovarian cysts at various stages of pregnancy, i.e., in the first, second, and third trimesters [16]. Only 1.2% of the women had an ovarian cyst with a maximum diameter of >30 mm. This figure is significantly lower than 5.4% published by Condous et al. which is probably a reflection of different population groups. The earlier in gestation a scan is performed, the more ovarian cysts, and in particular functional corpora lutea, will be detected. Borgfeldt and Andolf defined an adnexal lesion as either a simple cyst with the largest diameter of at least 25 mm or a complex cyst of any size. Adnexal lesions were found in 7.8% of the women [17]. Being a thin-walled vascular structure, such cysts are predisposed toward rupture; hemorrhage can be the primary event, but also a previous torsion can cause the cyst to rupture [18]. Rupture of adnexal torsion during pregnancy may also occur secondary to softening of the lesion following stromal decidualization [19]. Hemorrhage in the corpus luteum is a rare complication that occurs more frequently in younger women [20], especially when associated with pregnancy [21].

14.1.2 Ovarian Teratoma

The frequency of ovarian tumors is about 1/1000 pregnancies [7], and those which are malignant are found in about 1/15,000–1/32,000 pregnancies [15]. Mature cystic teratoma (dermoid cyst) is one of the most common benign ovarian neoplasms discovered during pregnancy (24–40%) [22, 23]. The word teratoma is derived from the Greek word *teraton*, meaning monster, and was used initially by Virchow in the first edition of his book on tumors, which was published in 1863 [22]. Since mature cystic teratomas are composed of all three germ cell layers, the term "dermoid" is a misnomer. The majority of these tumors occur during the reproductive years providing further support for the germ cell theory [22]. Benign cystic teratoma (BCT) is the most common benign ovarian neoplasm comprising 10–15% of all ovarian tumors. It occurs at all stages of life, the majority of cases being diagnosed between 20 and 30 years of age [4]. This fact makes it the most common tumor during pregnancy (22–40% of all ovarian tumors) [4]. In pregnancy, the risk of complications increases significantly including rupture, torsion, infection, and malignant degeneration. As BCT has a tendency to remain in the confines of the true pelvis, it could lead to dystocia and obstructed labor [4].

14.1.3 Other Ovarian Tumors

The age shift of childbearing women could cause the changing of the histological distribution pattern. Jubb reported 34 cases of primary ovarian carcinoma associated with pregnancy between 1882 and 1963 [24]; only 54% were of epithelial type [25]. Additional 22 cases between 1963 and 1988 revealed 27% to be of epithelial type [26, 27]. In contrast to those previous reports, Dobashi et al. showed that the most common histological types were 80% epithelial, 60% invasive, and 20% borderline tumors. Of note were the two clear cell carcinomas (20%), which is a relatively high incidence compared to other studies outside Japan; the incidence of ovarian clear cell carcinoma in Japan is the most frequent in the world [28]. The characteristic age group was 30–35 with a high incidence of nulliparity [24]. The age range in the study by Creasman et al. was 18–34, and around 50% were primigravidas [29]. Torsion is an important concern of pregnancy-associated adnexal masses and had a much higher incidence (13.8%) than malignancy (3.4%) [2].

14.1.4 Ovarian Endometrioma

Decidualization is the process of endometrial change caused by high progesterone levels which increase glandular epithelial secretion, accumulation of glycogen, and stromal vascularity. These changes create conditions which facilitate implantation and development of early gestation.

Formation of ectopic decidua (deciduosis) during pregnancy is a well-documented phenomenon that is caused by the effect of progesterone on the ectopic endometrium, such as in foci of endometriosis [30].

Ovarian endometriomas account for 4–5% of ovarian cysts diagnosed in early pregnancy [16] and up to 11.5% of all adnexal masses during pregnancy [31]. Endometriomas have features in common with neoplasia, such as clonal proliferation, which is consistent with the endometriosis disease theory, and are associated with subtypes of ovarian malignancy, such as endometrioid and clear cell carcinoma [19].

14.2 Clinical Presentation

Simple or functional cysts commonly do not cause symptoms, as well as other smaller adnexal masses. Most of these adnexal masses are diagnosed incidentally at the time of dating or first-trimester screening ultrasound [32]. Functional cysts of the ovary commonly do not cause pain unless the cyst presents as a cyst complication in a form of rupture, torsion, infection, or hemorrhage. Subjective symptoms were noted in 56.2% during pregnancy and in 6.8% during the puerperium [33]. If the tumor is large, it may cause pressure symptoms (mass effect), varying from discomfort, dyspnea [34], bladder irritability, etc. to actual pain. Both subjective symptoms and cyst complications during pregnancy and the puerperium were far more frequent with abdominal than with pelvic ovarian tumors, and more frequent with cysts of other sorts than with dermoids. Cyst complications occur in around 20% of patients [33].

Corpus luteum cysts more frequently attain a larger size than the follicular cysts. Corpus luteum cysts often produce a delay in the onset of the menstrual period, and when it occurs, it may be heavy in nature (*Halban's syndrome*). Because the cysts are usually larger than follicular cysts and associated with intraluminal bleeding, pain may be a common complaint. The cysts usually regress spontaneously and resolve in 4–8 weeks. Corpus luteum cysts are very vascular, and severe life-threatening hemorrhage may occur when they rupture. On the contrary, rupture of a follicular cyst may cause an acute onset of pain that is usually short-lived. The combination of a delayed menstrual period, acute pain, pelvic mass, and evidence of hemoperitoneum is strongly suggestive of a ruptured corpus luteum cyst.

Common symptoms of malignant ovarian tumors during pregnancy are excessive generalized enlargement of the abdomen and lower abdominal pain. Around 21% presents with an acute abdomen due to complications of the carcinoma such as rupture, torsion, or strangulation [24]. McKerron collected 1290 cases in 1903 and said that 80% of small tumors occupying the pelvis is found only upon pelvic examinations in labor [13]. The absence of symptoms in one-fourth of cases shows the necessity of most careful antepartum routine examinations [33]. The physical findings are often misleading. Hard semisolid dermoids or cystic tumors made tense by pressure may be mistaken for fibroids or vice versa. The abdominal distention with large flaccid cysts and fat abdomen may be most confusing. Ascites is common with cysts but rarely occurs with fibroids. Pelvic examination usually reveals diffuse pelvic tenderness, often lateralized to the side of the cyst, and a mass may be palpated. If a mass is palpable on pelvic examination, it should be characterized in terms of contour, firmness, size, location, and mobility. The rectovaginal examination should be done to palpate the uterosacral ligaments and cul-de-sac to assess for the presence of metastatic disease, nodularity, or obliteration of the cul-de-sac. If hemorrhage is severe, it may produce abdominal distention and shock.

14.3 Differential Diagnosis

The acute pain associated with rupture of a blood-filled corpus luteum cyst is indistinguishable from that of a ruptured ectopic pregnancy. A serum beta human chorionic gonadotropin (βHCG) level may be helpful in distinguishing these two entities. Differential diagnosis is presented in Table 12.1 (see Chap. 12).

14.4 Diagnosis

14.4.1 Laboratory Findings

WBC and CRP help to diagnose the infection and its severity. Hemoglobin and hematocrit help in the diagnosis of intra-abdominal bleeding and its severity. In early pregnancy or when the patient is still unaware of pregnancy, diagnosis between the hemorrhagic ovarian cyst and ruptured ectopic pregnancy is sometimes difficult. The distinction between these entities largely depends on the serum βHCG level. Assuming no intrauterine pregnancy is seen in an elevated serum βHCG level makes these findings strongly suggestive of the adnexal ring heralding an ectopic gestation, whereas a negative serum βHCG level makes a hemorrhagic ovarian cyst more likely [35].

If an ovarian tumor is suspected, tumor markers should be checked (Table 14.3). The role of tumor markers is limited in cases of cancer during pregnancy, or pregnancy after cancer, mainly due to their low specificity rate. Elevations are not always correlated with the presence of malignancy but are more often associated with normal physiologic changes of pregnancy. Moreover, obstetrical complications can induce even more variations. For example, elevated CA-125 has been associated with imminent miscarriage [36], and LDH is known to increase in cases of severe preeclampsia and HELLP syndrome (hemolysis, elevated liver function tests, low platelets) [37].

> Only CA-125 values can be raised during normal pregnancy, while all other tumor marker levels generally remain below the cutoff values [38]

Tumor markers are helpful for both establishing the diagnosis and monitoring response to treatment.

Table 14.3 Tumor markers in ovarian tumors

Tumor marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
βHCG	Embryonal carcinoma
	Choriocarcinoma
Inhibin A/B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
α-fetoprotein	Endodermal sinus tumor
	Embryonal carcinoma

CEA carcinoembryonic antigen, *HCG* human chorionic gonadotropin

14.4.2 Abdominal Ultrasound

If the patient is hemodynamically stable, pelvic and abdominal sonography is valuable. The diagnosis is easy if the cyst is in the pelvis, but it is often missed if the tumor is small and behind the uterus, when its presence may not be revealed until after labor. If the patient is stable, without symptoms and signs of peritonitis or massive bleeding, it is important to define if the mass is malignant. Three criteria are used to distinguish benign from malignant masses on sonography: tumor volume, cyst wall structure, and septa structure [32]. Malignancies of adnexal masses during pregnancy are commonly described only according to their complex ultrasound character, which has been criticized as an oversimplification and which has low positive predictive value for malignancies [39] and is unhelpful in distinguishing tumors of low malignant potential from benign neoplasms [5] because of morphological similarities. *Internal papillary excrescence* that can be visualized in 50% of malignancies [40] is an important sign. In any event, there are some pitfalls in applying the abovementioned criteria to adnexal masses in pregnancy. First, it is hard to obtain good images of adnexal masses after the 20th week of gestation, unless the mass is quite large; second, there may be technical difficulties in evaluating velocimetric features during pregnancy, as the vessels and blood flow surrounding the gravid uterus mainly have high velocity and low resistance characteristics with false-positive rate of nearly 50% [41]; and third, the major tumor type during pregnancy is of germ cell origin, whose ultrasound characteristics, although not necessarily different from those of epithelial origin tumors, could be incompatible with the scoring criteria developed for epithelial ovarian cancers. Significantly higher sonographic tumor growth rates are found in confirmed ovarian pregnancies. Even a growth of 0.35 cm/week has been defined [2].

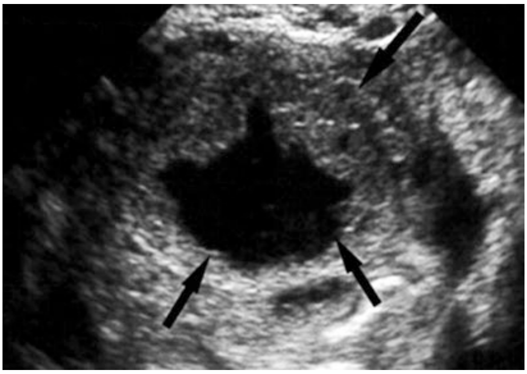

Fig. 14.1 Hemorrhagic ovarian cyst simulating a ruptured ectopic pregnancy in a 23-year-old woman with severe acute pelvic pain and a positive βHCG. Coronal right adnexal sonogram showing a mass with an irregular thick rind (*arrows*). This was mistaken for a ruptured ectopic pregnancy but was identified as a ruptured hemorrhagic cyst at laparoscopy. The patient had a concurrent very early intrauterine pregnancy. Reproduced with permission from [45]

The hemorrhagic ovarian cyst exhibits a myriad of sonographic appearances. Most commonly it is depicted as a rounded hypoechoic mass containing low-level echoes, fine strands, or septations; however, other patterns are seen so frequently that the hemorrhagic ovarian cyst has been termed "the great imitator" [42, 43]. Occasionally, a hemorrhagic ovarian cyst presents as a thick echogenic wall surrounding a central rounded echolucent area—a pattern remarkably similar to that of the *adnexal ring sign* (Fig. 14.1) of an ectopic pregnancy. The identification of an intrauterine gestational sac essentially excludes the diagnosis of ectopic pregnancy and may permit expectant management even when intraperitoneal bleeding has occurred [35, 44]. Elevated βHCG can be misleading. In such cases, intrauterine pregnancy should be ruled out (heterotopic pregnancy).

Sonographic and color Doppler of decidualized ovarian endometrioma consistently documented rapidly growing and abundantly vascularized intracystic excrescences. Conversely, the presence of septations or significant free fluid was never reported (Fig. 14.2).

Pyosalpinx has a very typical appearance of a thick wall cystic "sausage"-shaped structure with an incomplete septum.

Nearly one-fifth of the patients did not have their adnexal tumor discovered until the occurrence of tumor torsion or incidentally during CS, even though these tumors were of nonnegligible diameter. This underscores the possibility that some portion of patients with vaginal delivery could have failed to have their asymptomatic adnexal mass revealed, thus making the true denominator of these events during pregnancy unknown [2].

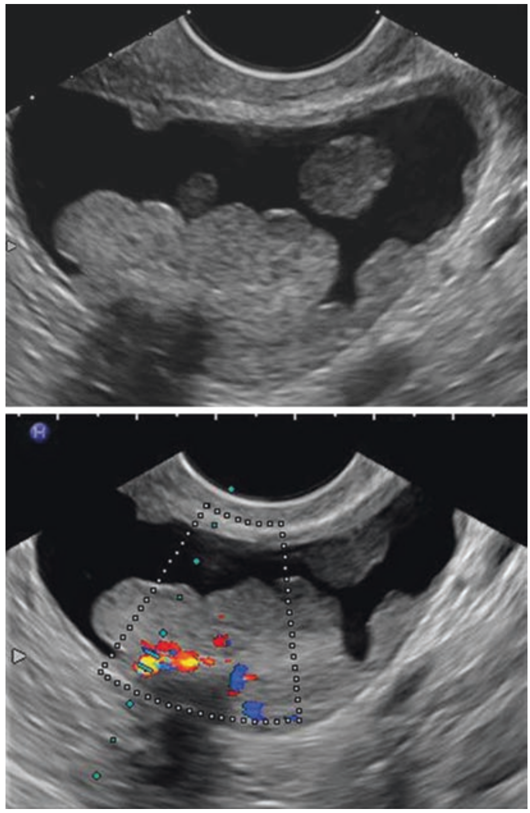

Fig. 14.2 Sonographic findings of ovarian endometrioma in pregnancy mimicking malignancy. The irregular solid part of the endometrioma protruding within the lumen of the cyst. Above this excrescence, an echogenic debris which was mobile under probe manipulation can also be noted (*upper panel*). Color Doppler detected multiple vascularization signals index within the solid part (*lower panel*). The resistance index was 0.37. Reproduced with permission from [46]

14.4.3 Abdominal MRI

MRI is generally considered safe in pregnancy and is the procedure of choice in certain conditions. It is better at distinguishing paraovarian

cystic lesions, which can then be managed conservatively, and also can provide better tissue characterization, allowing for more accurate evaluation of the large masses that are difficult to completely visualize by US. MRI can also determine the possible extent of malignancy and aid in the diagnosis of acute bowel processes such as appendicitis and inflammatory bowel disease [47]. However, the use of MRI in pregnancy should be judicious and solely for the clarification of an inconclusive US result.

14.5 Treatment

14.5.1 Introduction

Because complications of ovarian surgery are increased in pregnancy [48, 49], surgical management of ovarian cysts in pregnancy has been reconsidered [50]. Historically, pregnant women with persistent adnexal masses underwent elective removal of the masses in the second trimester [51]; this is no longer an acceptable practice in asymptomatic women, as surgical intervention, as either an emergency or after 24 weeks of gestation, is associated with a poorer obstetric outcome [8]. Obstetric complications include spontaneous miscarriage or preterm premature rupture of membranes [50].

14.5.2 Conservative Treatment

14.5.2.1 Observation

Asymptomatic

As only 0.13% of women with an ovarian cyst required acute intervention during pregnancy, the conclusion is that examining the ovaries at the time of a first-trimester scan is of limited value. With the advent of imaging techniques like MRI and transvaginal color Doppler, the expectant management has become much more common.

Early in pregnancy, ovarian enlargement less than 6 cm diameter is usually due to corpus luteum formation. Asymptomatic patients with simple unilocular cyst smaller than 6 cm in diameter and do not change need only periodic sonographic follow-up. Most of these resolve spontaneously [11, 52]. Corpus luteum cysts regress by 12–16 weeks. If the ovarian cyst is diagnosed in the first trimester, it is better to wait till 14–16 weeks: (1) the implantation of pregnancy is more secure, (2) the cyst may disappear spontaneously, (3) surgical access to the mass is much easier, and (4) if oophorectomy is done prior to this time, progesterone supplement should be administered.

Abdominal Pain

Those women requiring intervention will present with pain, while prior knowledge of the presence of a cyst may only increase anxiety even though the risk of complication is very low. If an apparently nonmalignant ovarian cyst is noted at the time of a first-trimester ultrasound examination, the woman should be offered a follow-up scan 6 weeks after the pregnancy has concluded. Although there are no randomized clinical trials to determine the optimal management of an adnexal mass in pregnancy, experience suggests that expectant management is safe and without serious adverse outcome for both mother and fetus [16].

Bleeding

In emergent settings, if a provisional diagnosis of hemorrhagic corpus luteum cyst with minimal hemoperitoneum can be made, most such cases may be best served by expectant management with serial clinical examination and hemoglobin measurements [20].

Growing understanding of the natural history of *borderline ovarian tumors* allows a more conservative approach in their surgical management, preserving fertility in many young women [53]. The problem with borderline ovarian tumors is the inaccuracy of preoperative diagnosis. Histologically confirmed diagnosis can be found in only 33% with sonographic appearance and the presence of papillary projections that were nonvascular on color Doppler [53]. The additional surgical dilemma is the size of the tumor. Despite benign characteristics, it can have a high probability of torsion [53]. This highlights the difficulty in classifying some ovarian masses, and it is well accepted that 10% of adnexal

masses are extremely difficult to classify [54]. Despite the fact that the borderline lesions in some studies were managed surgically [53], there is evidence to suggest that expectant management of such ovarian cysts is an option. After the pregnancy, these patients underwent surgery [16, 54].

A similar problem is with *decidualized ovarian endometriomas* during pregnancy. On the one hand, an expectant management strategy appears reasonable considering that pain symptoms are generally improved during pregnancy and that surgery is more demanding and risky due to the presence of the enlarged and pregnant uterus. On the other hand, concerns have been recently raised regarding the accuracy of sonography in pregnancy. Of the 27 published cases, 19 (70%) were managed surgically, 4 of which were delayed till CS with concomitant cyst excision; 8 cases were managed conservatively through serial monitoring of the cyst, which spontaneously regressed following delivery [55].

14.5.2.2 Ultrasound-Guided Aspiration

Aspiration of simple ovarian cysts during pregnancy is safe and may prevent the need for surgical intervention; in some cases, this will be the definitive treatment [56]. Neither anesthesia nor analgesia is required for such intervention. The ultrasound-guided aspiration for the relief of pain generated by simple ovarian cysts in nonpregnant women can be performed either transvaginally or transabdominally depending on the location of the cyst [57]. After 14 weeks of gestation, the uterus is an abdominal organ, and as a result, the ovaries are more easily targeted transabdominally. If the pain persists after the procedure without other symptoms or complications, a laparoscopic ovarian cystectomy after delivery is indicated [16]. Fine-needle aspiration is not appropriate if the cyst has any suspicious morphological features. It is not a common diagnostic problem because the frequency of ovarian cancer in pregnancy is reported to be 1/15,000–1/32,000 pregnancies [15].

14.5.3 Surgical Treatment

Operative treatment is oriented on the treatment of complications of cysts associated with pregnancy. In Barrett's series from 1913, in which expectant treatment of the tumor was carried out, the maternal mortality was 18.4%, as against 2% in patients treated surgically [58]. Indications for the operation are in Table 14.4 [51]:

Adnexal/cyst torsion is described in Chap. 12. Intrauterine growth retardation may be either due to the prominent vascularity of the tumor, originating from the ovarian vessels, or due to the compressive effect of the tumor on the uterine blood supply [59].

14.5.3.1 Emergency Laparotomy

If the patient is hemodynamically unstable or the diagnosis is in question, exploratory surgery is required. In hemodynamically unstable patient, emergency laparotomy, not laparoscopy, is indicated because definitive surgery is mandatory in the shortest possible time period. The second indication for emergency laparotomy is fetal distress when after CS, definitive surgery is performed. The third indication is obstructed labor due to ovarian cyst/tumor when, again, CS followed by definitive surgery is done.

Table 14.4 Indications for surgery of complex cysts in pregnancy

Emergent operation	Early elective operation
Torsion of the cyst/adnexa	Mass >6 cm until the second trimester unless uterine leiomyoma
Rupture of the cyst	
Infected cyst	
Suspected/proven malignancy	
Urinary retention due cystic impaction	
Dyspnea due to a giant tumor	
Obstructed labor	
Fetal malpresentation	
Intrauterine growth retardation	

If rupture and bleeding do occur but without hemodynamic instability, diagnostic and therapeutic laparoscopy is appropriate.

Hemorrhagic Corpus Luteum

If a provisional diagnosis of hemorrhagic corpus luteum cyst with minimal hemoperitoneum can be made, most such cases may be best served by expectant management [20]. However, once massive hemorrhage from ruptured corpus luteum cysts occurs, it can be a life-threatening condition that requires emergent surgical intervention [21]. With advances in laparoscopic surgical procedures and the development of surgical equipment, laparoscopic treatment of a ruptured corpus luteum cyst with hemoperitoneum is highly desirable [60, 61]. Further, utilizing intraoperative autologous blood transfusion, transfusion of bank blood can be avoided even in cases of massive hemoperitoneum due to ruptured corpus luteum cyst in patients with ectopic pregnancy [60, 61].

Ovarian Teratoma

Ruptured BCT of the ovary mimicking gynecological malignancy is uncommon and could be misdiagnosed [62]. Intra-abdominal peritoneal seedlings, adhesions, and/or masses are a frequent sequela. In most such cases, abdominal seedlings are essential of mature neuroglial elements, and the long-term survival rate is good. Recognition of a dermoid tumor associated with glial seedling is important to avoid unnecessary debulking surgery. Following postoperative adhesions, fibrous bands, or obstructions, conservative management seems to have a good prognosis.

Obstructed Labor

As for any other cause, indication for the emergent CS and ovarian mass operation during pregnancy is the risk of obstruction/proven obstruction of labor by ovarian mass, which is 17–21% [47].

14.5.3.2 Elective Laparotomy

Indications for early elective operations are cysts more than 10 cm in diameter due to an increased risk of malignancy, rupture, or torsion. Management of cysts ranging 5–10 cm is controversial. If the cysts contain septa, nodules, papillary excrescences, or solid components, then surgical intervention is recommended.

Ovarian Teratoma

Treatment of suspected ovarian teratoma is surgical removal as soon as possible after diagnosis to avoid complications. They may be responsible for torsion, rupture, and obstruction during labor. Over 200 cases of BCT in pregnancy have been reported, many of them ruptured spontaneously or iatrogenically. In a review of 47 cases, Kocak et al. reported that during cyst extraction, minimal spillage occurred in 42.5% of cases and none developed chemical peritonitis [63]. Rupture is rare, but once it has occurred, it can cause complications such as chemical or granulomatous peritonitis mimicking advanced ovarian malignancy [4, 62]. All efforts should be made to avoid rupture or leakage of cyst fluid during the operation. If it happens before or during the operation, copious saline washing should be performed to minimize chemical peritonitis and its sequela, including further surgeries to treat the complications [64, 65]. In granulomatous peritonitis after ruptured ovarian teratomas, numerous nodules of mature glial tissue implant on a widespread area of the peritoneum. This diffuse peritoneal reaction mimics advanced ovarian malignancy, and commonly surgical staging is performed [4, 62].

When BCT is found incidentally in the first trimester of pregnancy, surgical removal should be performed at 14–16 weeks of gestation to avoid the risk of damage to the corpus luteum. If the diagnosis of BCT occurs at 16–22 weeks, surgery should be performed as soon as possible. If it is first discovered after 22 weeks of pregnancy, the treatment may be deferred until delivery [4].

14.5.3.3 Minimally Invasive Surgery

General Considerations

Pregnancy is no longer an absolute contraindication for laparoscopic procedures. With increasing gestational age, the uterus rises out of the pelvis,

and there is an increasing chance of injury while inserting the Veress needle. Generally, open access (Hasson) or blind Palmer's point entry is recommended. This avoids the risk of penetrating injury to the pregnant uterus by either the Veress needle or the trocar cannula. Ovarian tumor or cyst can be easily removed till 28 weeks of gestation; thereafter its manipulation is difficult and may precipitate preterm labor.

The major advantages of laparoscopy are magnification and panoramic view of the pelvis resulting in reduced intraoperative uterine manipulation which may lead to decreased postoperative uterine irritability, miscarriage rate, and preterm labor up to 50% of third-trimester cases with an open approach. In addition, the cosmetic results are much better, and the discomfort of stretching and distention of the laparotomy scar due to the rapidly growing uterus is avoided. Therefore, lower rates of dehiscence or herniation during labor are present. The laparoscopic approach provides the benefits of a shortened hospital stay and reduced postoperative pain minimizing fetal exposure to narcotics.

Gasless Laparoscopy

In an attempt to overcome the potential adverse effects of pneumoperitoneum on the fetus, gasless laparoscopic surgery (GLS) has been developed during the 1990s [66, 67]. GLS in pregnancy has comparable outcomes to conventional CO_2 laparoscopy, but it is associated with some advantages. Hypercarbia and increased intraperitoneal pressure due to CO_2 insufflation are avoided. Operations can be performed in epidural anesthesia [68].

There are two basic lift systems. The *subcutaneous lift system* [66, 68] has some advantages with respect to the *full-thickness wall lift* [67]. First, the surgeon can avoid injury to the gravid uterus, thus reducing the risk of abortion. Second, the subcutaneous lift system can be applied to all patients, regardless of any history of abdominal surgery or any unexpected adhesions. Another positive feature of the subcutaneous lift system is the elimination of trauma to the peritoneum, which could cause pain and result in adhesions. Up to 2013, there were more than 30 cases of nonemergent GLS, adnexal mass operations during pregnancy [68–71].

Elective Robotic and/or Single Site Surgery

Robotic resection of adnexal masses during pregnancy appears both safe and feasible, with similar surgical outcomes when compared with a historic laparoscopic cohort. The robotic cohort had a significantly shorter length of hospital stay and estimated blood loss [72]. Single site/single port surgery for adnexal masses in pregnancy demonstrated the feasibility, safety, and putative benefits. Resected ovarian mass can be extracted through the same abdominal wall incision where the port was introduced eliminating the need for additional abdominal wall trauma [73, 74]. This is especially important for the masses that cannot be decompressed or aspirated (see Sect. 14.5.3.3). Principles of single port surgery are described in Sect. 12.8.3.

> *Laparoscopy is safe and effective treatment in gravid patients with symptomatic ovarian cystic masses. Observation is acceptable for all other cystic lesions provided ultrasound is not concerning for malignancy and tumor markers are normal. Initial observation is warranted for more cystic lesions less than 6 cm in size.*
>
> SAGES, 2011 [75]

Cystectomy

Laparoscopic cystectomy (Fig. 14.3) in pregnancy was first reported in 1991 by Nezhat et al. [76]. Conservative surgical therapy consisting of removing the cyst and coagulating its base is standard therapy. Large cystic masses may require decompression/aspiration to fit through a small incision. By decompressing a cyst into a laparoscopic bag, spillage can be minimal or nonexistent. Copious irrigation also helps to keep the residual content to a minimum (see Sect. 14.5.3.2). After cystectomy, the ovarian incision can be left open or approximated by three techniques:

- Fine monofilament suture of the edges.
- Tissue glue.
- Coagulation of the ovarian cortex adjacent to the surface.

Stitching is necessary to avoid adhesions between the raw ovarian surface and the raw peritoneal surface left after bowel adhesiolysis in the left adnexa [77].

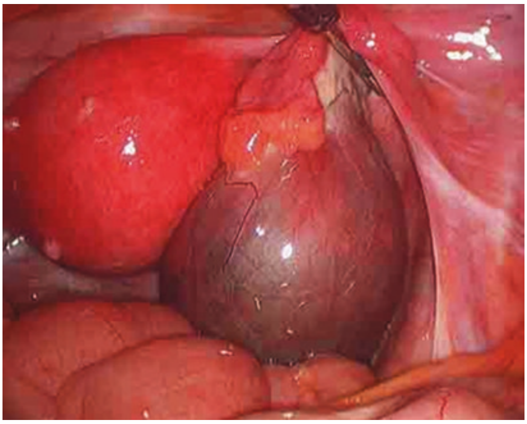

Fig. 14.3 Laparoscopic cystectomy of a dermoid cyst at 16 weeks of pregnancy. Reproduced with permission from [78]

The complete diagnostic–therapeutic algorithm of unruptured ovarian cysts in pregnancy is presented in Fig. 14.4.

14.5.4 Anesthetic and Perioperative Management

14.5.4.1 First Trimester

If the corpus luteum cystectomy or ovariectomy is performed during the first trimester, the patient should receive 17-α hydroxyprogesterone caproate 250 mg intramuscularly weekly during 4 weeks (Proluton depot) as progestogen support for the pregnancy [80].

14.5.4.2 Bilateral Ovariectomy

As early as 1931 there were reports where both ovaries have been removed and the pregnancy has normally continued [81]. It is usually stated that the corpus luteum is indispensable to pregnancy for the first 2 months and removal during that time precipitates abortion.

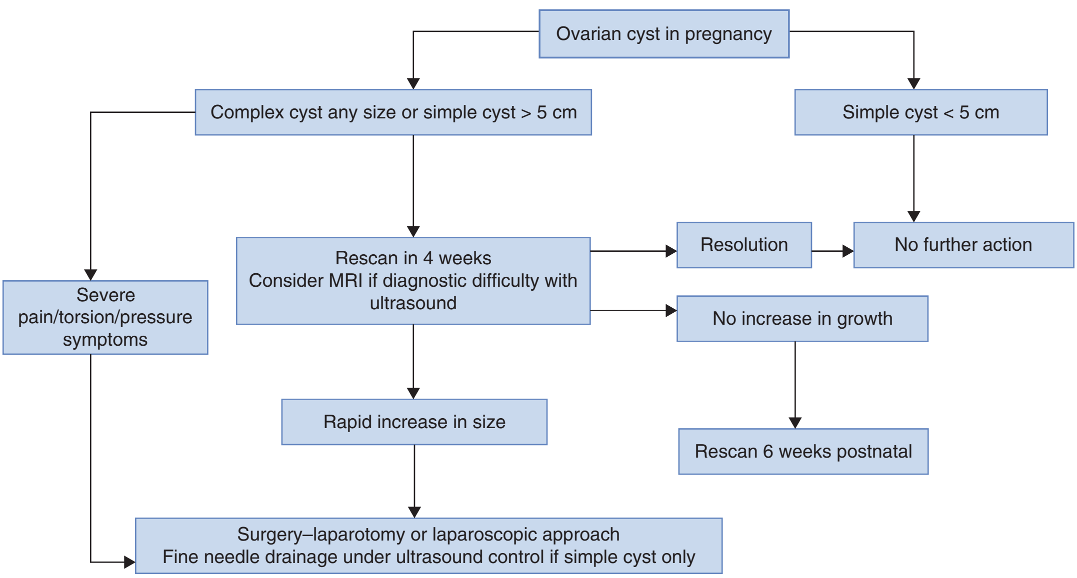

Fig. 14.4 Diagnostic–therapeutic algorithm of unruptured ovarian cyst in pregnancy. Reproduced with permission from [79]

> If it is necessary to remove a corpus luteum of early pregnancy (prior to 12 weeks) or bilateral ovariectomy is indicated, progesterone replacement is advisable following surgery

14.5.4.3 Adjuvant Chemotherapy

If the adnexal mass turns out to be ovarian cancer, the treatment of the pregnant woman is similar to that of the nonpregnant women depending on the stage, gestational age, as well as staging and grade of the tumor [82]. In certain circumstances, it may be justified to remove the tumor only and await fetal maturation, while in some cases chemotherapy may even be given while awaiting pulmonary maturation [83, 84].

14.5.4.4 Anesthetic and Perioperative Management

See Chap. 21.

14.5.4.5 Prevention and Treatment of Preterm Labor

See Chap. 23.

14.6 Prognosis

14.6.1 Maternal Outcome

14.6.1.1 Continuation of Pregnancy

There are several possible pathophysiologic mechanisms that can interfere with the normal continuation of pregnancy. First is hormonal influence. The problem could arise if bilateral adnexectomy/ovariectomy is performed. Fortunately, there are cases with normal further pregnancy after that procedure (see Sect. 14.5.4.2). Second is obstruction of labor or pregnancy with the tumor or uterus incarcerated in the pelvis. The third is a secondary infection of primary ovarian pathology. Graefe stated that ovarian cysts produce abortions or premature labor in 14–20% of cases.

14.6.1.2 Malignant Tumors

In 21 of the reviewed cases by Jubb, the diagnosis was followed by immediate laparotomy and unilateral oophorectomy. Fourteen of these patients had no further treatment. In the 33% of reexplored patients, no residual carcinoma was found. Unfortunately, there is no record of grading of the carcinoma, and follow-up was inadequate. Because of this, the figure for the 5-year survival rate of nearly 60% is unreliable [24]. All of Creasman et al.'s more radically treated patients with stage IA ovarian carcinoma were well at 5 years, and they claimed that this demonstrated the value of a more radical approach to treatment. It would seem equally likely that the good survival rates reflected early diagnosis at routine antenatal examinations of patients. It is obvious that sacrifice of the pregnancy does not improve the maternal prognosis and that unilateral oophorectomy can be employed [29].

14.6.2 Fetal Outcome

14.6.2.1 Fetal Morbidity

There is evidence to suggest that laparoscopy and laparotomy do not differ with regard to the fetal outcome—fetal weight, gestational age, growth restriction, infant survival, and fetal malformations [47, 83, 85, 86]. It confirms the thesis that the underlying pathology, not the procedure itself, influences fetal morbidity and mortality. There is only 1 long-term follow-up (1–8 years) study, with 11 cases, and no evidence of developmental or physical abnormalities in the resultant children after acute but nonobstetric laparoscopic surgery during pregnancy [87].

14.6.2.2 Fetal Mortality

There are no significant differences in fetal outcomes between patients undergoing emergency laparotomy (fetal mortality 18%) and those having scheduled laparotomy (fetal mortality 23%) [5]. Nonemergent GLS, adnexal mass operations during the second trimester were completed without a fetal loss [68].

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Ruptured Ectopic Pregnancy

15

Abstract

Ectopic pregnancy is one of the most common nonsurgical abdominal conditions during pregnancy. Unfortunately, most of these presentations are during early pregnancy when the conceptus is not developed for the independent life and is also not "viable." Preoperative and early diagnosis is common due to the specific clinical presentation and the routine use of βHCG for women of reproductive age presenting with pain in the lower abdomen. Depending on the fetal status and severity of bleeding, both conservative and operative interventions are available and successful. Biggest diagnostic and therapeutic dilemmas arise in patients with heterotopic or advanced abdominal pregnancy. The clinician should always look for intrauterine pregnancy preoperatively even when ectopic pregnancy is confirmed. Advanced abdominal pregnancy poses a real intraoperative problem due to adherence of the placenta to surrounding organs and tissues, and insisting on its complete removal can cause significant and sometimes unstoppable bleeding.

15.1 Ectopic Pregnancy in General

If a woman with child be bled, she will have an abortion, and this will be the more likely to happen, the larger the fetus.

Hippocrates, 400 BC

If one is confronted with a pelvic condition that follows no rules and conforms to no standards, he should think of ectopic pregnancy and pelvic tuberculosis.

Howard Atwood Kelly

15.1.1 Incidence

The rate of ectopic pregnancy has increased dramatically. It is defined as implantation of a fertilized egg outside the uterine endometrium. The *Centers for Disease Control and Prevention* (CDC) reported that the number of ectopic pregnancies quadrupled from 17,800 in 1970 to 88,000 in 1989 [1]. This is an increase in rate from 4.5 to 16.8/1000. In 1992, CDC estimated the US ectopic pregnancy rate at 1.97% of all pregnancies [2] and is rising [3]. Ectopic pregnancy caused an estimated 876 US deaths

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_15

between 1980 and 2007 [4]. The prevalence of ectopic pregnancy among women who go to an emergency department with first-trimester bleeding, pain, or both ranges 6–16% [5]. An ectopic pregnancy occurs with some seasonal variation and is most common in June and December [6]. The reason is unclear; the authors postulated that reproduction is seasonal, depends on photoperiod and temperature, and varies with different latitudes.

15.1.2 Risk Factors

If the egg is too big, or if the diameter of the tuba Fallopiana is too small, the egg stops and can get no farther, but shoots forth and takes root there.

Pierre Dionis, 1718

The overall risk is approximately 1/200 pregnancies but may be increased 20- to 100-fold in certain subsets of women [6]. Risk factors are presented in the Table 15.1.

As many as 50% of Fallopian tubes removed because of an ectopic pregnancy show prior inflammatory disease. The increased incidence of the pelvic inflammatory disease is thought to be a major factor in the increased numbers of ectopic pregnancies. Although the risk of pregnancy is very low with a tubal ligation, if a pregnancy does occur, there is a significantly higher risk of the gestation being an ectopic one. Of those pregnancies occurring after tubal ligation, 10–50% are ectopic, which represents a 20- to 100-fold increased risk [6]. The intrauterine contraceptive device is found in up to 68% of ovarian pregnancies, and its frequency is also higher in the case of endometriosis, assisted reproductive technology, and emergency contraception [7].

Table 15.1 Risk factors for ectopic pregnancy [3, 7]

Pelvic inflammatory disease
Previous tubal (ectopic) pregnancy
Current intrauterine device use
Previous tubal surgery, including tubal sterilization
Previous infertility treatments
Endometriosis
Emergency contraception

15.1.3 Classification

15.1.3.1 Tubal Pregnancy

More than 95% of ectopic pregnancies implant in the Fallopian tube. Pregnancies can grow in the fimbrial end (11%), the ampulla (70%), the isthmus (12%), and the cornual and interstitial part of the tube (2%) [8]. The tubal ectopic pregnancy is caused by a combination of retention of the embryo within the Fallopian tube due to impaired embryo-tubal transport and alterations in the tubal environment allowing early implantation [9].

15.1.3.2 Non-tubal Ectopic Pregnancy

Two percent of ectopic pregnancies occur in the ovary, cervix, or intra-abdominally (Fig. 15.1) [8].

Ovarian Pregnancy

An ovarian pregnancy is differentiated from a tubal pregnancy by the *Spiegelberg criteria* described in 1878 [11]:

- Gestational sac is located in the region of the ovary
- Ectopic pregnancy is attached to the uterus by the ovarian ligament
- Ovarian tissue in the wall of the gestational sac is proved histologically
- Fallopian tube of the involved side is intact

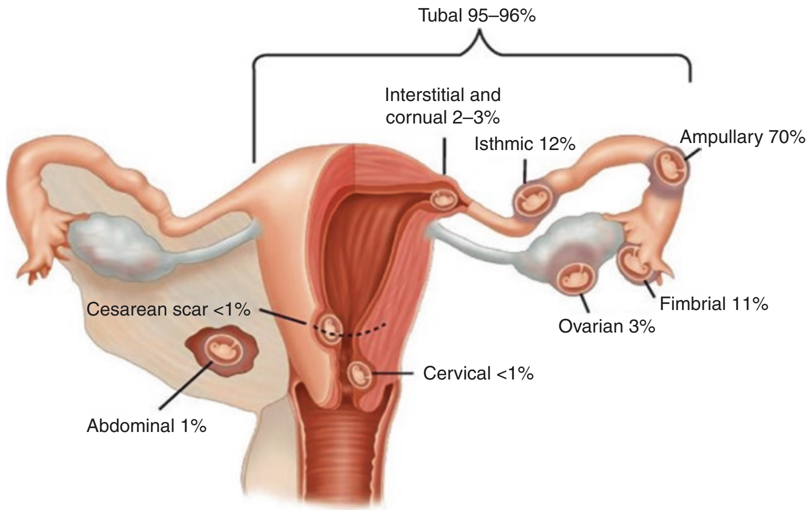
Abdominal Pregnancy

Intraperitoneally located fetus is typically not viable, very rarely; a live baby has been delivered from an abdominal pregnancy. In such a situation, the placenta sits on the intra-abdominal organs or the peritoneum and has found sufficient blood supply. This is generally bowel or mesentery, but other sites, such as the renal (kidney), liver, or hepatic artery or even aorta have been described. For details about abdominal pregnancy, see Sect. 15.3.

15.1.3.3 Heterotopic Pregnancy

Heterotopic pregnancy is defined as the coexistence of intrauterine and extrauterine gestation. The incidence was originally estimated on a theoretical basis to be 1/30,000–1/50,000 spontaneous pregnancies. However, more recent data

Fig. 15.1 Sites and incidence of implantation in ectopic pregnancy following natural cycles (*left*) and assisted reproductive technology (*right*). Reproduced with permission from [10]



indicate that the rate is higher due to assisted reproduction and is approximately 1/7000 overall and as high as 1/900 with ovulation induction [12]. Most commonly, the location of ectopic gestation in a heterotopic pregnancy is the Fallopian tube. However, cervical and ovarian heterotopic pregnancies have also been reported [13, 14]. The majority of the reported heterotopic pregnancies are of singleton intrauterine pregnancies. Triplet and quadruplet heterotopic pregnancies are extremely rare [15, 16]. These can be multiple and can be seen frequently with assisted conceptions.

15.1.3.4 Persistent Ectopic Pregnancy

A persistent ectopic pregnancy refers to the continuation of trophoblastic growth after a surgical intervention to remove an ectopic pregnancy. After a conservative procedure that attempts to preserve the affected Fallopian tube such as a salpingotomy, in 15–20% the major portion of the ectopic growth may have been removed, but some trophoblastic tissue, perhaps deeply embedded, has escaped removal and continues to grow, generating a new rise in βHCG levels [17]. After weeks, this may lead to new clinical symptoms including bleeding. A decline of less than 55% at day 3 predicts persistent ectopic pregnancy and may select early cases for second-line methotrexate therapy [18]. βHCG dynamics in the week before salpingotomy and bleeding activity at surgery may identify patients who are the most likely candidates for persistent ectopic pregnancy after laparoscopic linear salpingotomy [17].

15.1.4 Clinical Presentation

Textbooks from the first half of the twentieth century claimed that the diagnosis of ectopic pregnancy based on clinical criteria (of gastric and mammary symptoms of pregnancy, cessation of the menstrual cycle, palpation of a tumor next to an enlarged uterus, ballottement in the tumor, and purple discoloration of the vagina) had false preoperative diagnosis of a ruptured ectopic pregnancy of 20%, while the diagnosis of an unruptured ectopic pregnancy was virtually impossible [19].

15.1.4.1 Medical History

Few of the conditions which come under the notice of the gynecologist are of greater interest in diagnosis than extrauterine gestation. Occasionally, cases present with features so striking and so characteristic that their nature is readily recognized. But this is not always the case, for the clinical features may be so complex as to puzzle the most experienced observers. And not only are the clinical features complex, they are also subject to extraordinary variation in character and severity, and it may be difficult to believe that the same pathological condition has given

rise to them all. A quote from Howard A. Kelly seems timely, that *if one is confronted with a pelvic condition that follows no rules and conforms to no standards, he should think of ectopic pregnancy and pelvic tuberculosis* [20]. The explanation of these difficulties lies in the fact that the symptoms associated with extrauterine gestation arise, not directly from the presence of the growing ovum in the Fallopian tube, but from certain secondary lesions, either traumatic or inflammatory, which supervene. These *secondary lesions* may be briefly enumerated as [21]:

- Intraperitoneal flooding from tubal abortion or rupture
- Intratubal bleeding leading to acute distention of the tube, the abdominal ostium being sealed
- Slowly progressive or recurrent hemorrhage leading to the formation of encysted collections of blood (pelvic hematoma, in the broad ligament, pelvic hematocele, in the pouch of Douglas, peritubal hematocele, around the abdominal end of the tube)
- Infection of the gravid tube or of an encysted collection of blood leading to suppuration

Until these secondary lesions are produced, extrauterine pregnancy gives rise to no more local or general disturbance than does an early pregnancy in the uterus. An important symptom associated with this phase, a brief period of amenorrhea, is the most useful aid in diagnosis, but it is not always present. When a healthy adult woman, who is usually regular, goes for 2–3 weeks over the expected date of her period, there is a "strong presumption of pregnancy," but at this time, there is nothing to indicate whether the pregnancy is uterine or extrauterine. In the latter case, however, amenorrhea is of very brief duration, seldom more than 7–8 weeks, and then gives place to hemorrhage. In 30% of the cases, there is no amenorrhea at all. As it is quite unusual for an extrauterine gestation to continue undisturbed beyond the end of the second month, there is consequently no time for the appearance of other general symptoms of pregnancy. But occasionally, morning sickness and early breast changes may be present.

When the course of the gestation becomes interrupted by any of the occurrences mentioned above, the clinical features undergo rapid transformation, and symptoms of extrauterine pregnancy appear—those which result from the interruption of the pregnancy by injury to the developing ovum or to its containing sac. These symptoms, which are regarded as *secondary symptoms*, are subject to great variation in their character and intensity in correspondence with the nature of the lesion which has given rise to them. The occurrence which is the simplest and the most easily recognized is *intraperitoneal flooding*; the symptoms which attend it are uniform and characteristic, and when a clinical history of amenorrhea can be obtained and a careful pelvic examination made, mistakes are hardly possible. Perforation of a hollow viscus, such as the stomach, duodenum, or gall bladder, is the only condition for which it is at all likely to be mistaken, even under circumstances unfavorable for diagnosis. *Hemorrhage* from the uterus is a secondary symptom of extrauterine gestation which is constantly present. If no period of amenorrhea has occurred, it forms the initial symptom, and if there has been amenorrhea, it succeeds it. In the great majority of cases, it is the earliest indication of anything wrong, but as the same thing frequently occurs from disturbance of a uterine pregnancy, little importance is usually attached to its appearance by either the patient or her doctor. The hemorrhage is slight or moderate in degree, sometimes continuous, sometimes irregular; it is usually dark, thick, and syrupy in appearance. It may continue for several weeks if the patient is not relieved by the operation. The bleeding is no doubt due to separation and discharge of the uterine decidua, sometimes complete, more often in fragments; but in the majority of cases, the pieces of membrane do not attract attention. This attempt on the part of the uterus to throw off its decidua when the tubal ovum has been damaged is the most interesting phenomenon. Some reflex mechanism is initiated which excites uterine contraction insufficiently powerful to detach portions of the membrane from the uterine wall and so gives rise to hemorrhage, which continues until the whole of the decidua has been expelled. It is

possible that at the commencement some of the blood which escapes from the uterus may have made its way there from the gravid tube through the interstitial portion. In cases submitted to an operation, the hemorrhage always ceases in a few days after the removal of the tube, and if portions of decidua have been retained, these give rise to persistent bleeding, as is so often the case in uterine abortion.

The effects produced by the rapid effusion of a large quantity of blood into the peritoneal cavity are, in the order of their occurrence [21]:

1. Acute abdominal pain
2. Fainting and the constitutional signs of hemorrhage
3. Shock, attended by vomiting and lasting for several hours

No matter what may be the nature of the secondary lesions occurring in a case of tubal pregnancy, these two symptoms are common to them all—uterine hemorrhage and pain. The pain has certain characteristics. It is almost always sudden in onset, and usually spontaneous, although muscular effort, such as lifting something heavy or the act of defecation, may appear to excite it; it is always severe and often of the most intense character; it affects at first the whole abdomen but later may become localized; it is frequently attended with vomiting and other signs of shock, sometimes with faintness or actual syncope; after lasting acutely for several hours, it subsides and thereafter may recur at varying intervals of a few days or a week, until several attacks have been sustained; sometimes continuous pain without exacerbation follows the first attack. The initial attack of pain is almost always due to hemorrhage; the subsequent attacks have a more complex origin. But pain bearing the broad characteristics described above is a constant symptom of extrauterine gestation. In cases not immediately submitted to an operation, recurrent attacks of intense pain may occur from repeated intraperitoneal hemorrhages. The classic signs of hemoperitoneum except abdominal pain include shoulder pain caused by irritation of the phrenic nerve which courses along the undersurface of the diaphragm, an urge to defecate, and syncope even in the absence of hypovolemia.

Rupture of ovarian pregnancy classically occurs during the first trimester and is preceded by pain corresponding to distention of the ovarian capsule. In developed countries, due to early diagnosis, only 8–21% of ovarian pregnancies are observed with hemodynamic shock [22].

Simultaneous intestinal obstruction with ectopic pregnancy is described in detail in the Sect. 7.12.2. Subjective symptoms of pregnancy may also be present, such as breast tenderness and emesis gravidarum.

15.1.4.2 Physical Examination

Cullen's sign (Fig. 15.2) is the bluish-black appearance around the umbilicus, unassociated with any history of injury, together with a definite uterine history usually typical of the slow tubal abortion type of bleeding. Although Cullen first described the sign in 1918 and labeled it a new sign in ruptured extrauterine pregnancy [23], discoloration of the umbilicus due to the presence of peritoneal extravasations had been previously reported by Ransohoff in 1906. This author described jaundice of the umbilicus in a patient with a ruptured common bile duct, and

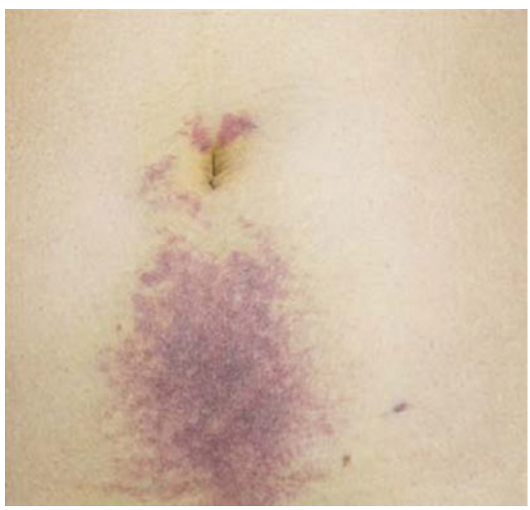


Fig. 15.2 *Cullen's sign* is a bluish-black appearance around the umbilicus; extension does not depend on the amount of bleeding but the duration of the primary process and other undetermined factors. Reproduced with permission from [26]

in 1909, Hofstatter observed a blue discoloration of an umbilical hernia (*Hofstatter's sign*) in a patient with a ruptured tubal gestation. However, the discoloration in Hofstatter's case was not due to ecchymosis but rather to transmission of the color of the blood through the thinned-out semi-transparent hernia.

The notion that the presence of blood in the abdominal wall might be responsible for these signs was first explored by Meyers et al., who used computed tomography [24]. They defined the anatomy of various retroperitoneal spaces and compartments, revealing that there is a direct extension of hemorrhagic fluid from the posterior pararenal space to the lateral edge of the quadrates lumborum muscle, where a defect in the transversalis fascia permits access to the abdominal wall musculature. The intramuscular hemorrhagic fluid then presumably reaches the subcutaneous tissues via interruptions in muscular continuity. Cullen's sign results from the tracking of blood along the round ligament to the umbilicus. The portal of entry to the round ligament complex from the retroperitoneum is via the gastrohepatic ligament to the falciform ligament at the inferior-posterior liver edge [25]. In turn, the falciform ligament contributes to the connective tissue tube covering the round ligament (obliterated left umbilical vein) as it passes to the umbilicus.

The appearance of periumbilical ecchymosis (Fig. 15.2) is a rare observation, and when present, it is a late manifestation of intraperitoneal hemorrhage. In Cullen's case, the discoloration began 1 week after the onset of pain. Undoubtedly, prompt surgical treatment prevents the development of the sign in many cases. It is possible that in some cases the sign appears after the operation without being observed preoperatively. One also wonders how many patients with tubal abortion, who undergo spontaneous resolution without operation, may develop the sign and never come under medical observation. The degree of discoloration, or its presence, does not seem to be related to the amount of bleeding but rather to its duration and to other as yet undetermined factors (Table 15.2).

Table 15.2 Conditions associated with non-iatrogenic Cullen's sign

Acute pancreatitis
Pancreatic trauma
Ruptured ectopic pregnancy
Ruptured aortic/iliac aneurysm
Ruptured spleen
Perirenal hematoma/bleeding
Ruptured common bile duct
Perforated duodenal ulcer
Hepatocellular carcinoma
Hepatic lymphoma
Amebic liver abscess
Metastatic thyroid cancer
Rectus sheath hematoma

Physical examination is variable, and adnexal masses are often not palpable [27, 28]. Tachycardia is not always present. Atypical physical findings include a paradoxical bradycardia [29], fever [30], and uterine enlargement suggestive of an IUP [30].

Some patients present with rectal bleeding as a sign of colorectal communications (infiltration) of ectopic pregnancy (see Sect. 11.8).

15.1.5 Differential Diagnosis

Differential diagnosis of Cullen's sign includes several conditions. Periumbilical cellulitis typically causes blanching erythema that is warm to the touch. *Sister Mary Joseph's sign* (nodule), or metastatic spread of an intra-abdominal malignancy to the umbilicus, may present with thickening and erythema of periumbilical skin or as a palpable mass lesion around the umbilicus [31]. Subcutaneous administration of heparin may result in abdominal wall ecchymoses, which are typically distant from the umbilicus. Patients with psoriasis may develop periumbilical erythema with a silvery scale that bleeds on removal (*Auspitz's sign*). Endometriosis with umbilical involvement accompanied by hemorrhage in conjunction with the menstrual cycle may occur rarely. Ulceration of a recanalized umbilical vein in the setting of cirrhosis may cause periumbilical skin darkening [32].

15.1.6 Diagnosis

Heterotopic pregnancy can have various presentations. Before the symptoms occur it should be considered more likely: (1) with persistent or rising chorionic gonadotropin levels after dilatation and curettage for an induced/spontaneous abortion, (2) when the uterine fundus is larger than for menstrual dates, and (3) when more than one corpus luteum is present in a natural conception. There are two symptomatic presentations. One is when the intrauterine pregnancy (IUP) is discovered later than the ectopic, mainly because of the typical clinical presentation of ectopic pregnancy before the woman is aware of the pregnancy. Another is abdominal pain/acute abdomen/hemoperitoneum/hemorrhagic shock in a woman with known early pregnancy. Difficulty in diagnosis in this second form is due to ultrasound findings of normal intrauterine pregnancy and rare incidence of additional ectopic pregnancy.

15.1.6.1 Laboratory Findings

The urine βHCG assay is sensitive to ≤25 mIU/mL, and more than 95% of patients with ectopic pregnancies have a positive test [33]. Transvaginal ultrasound has replaced transabdominal for ectopic pregnancy diagnosis and early screening for an IUP because it can visualize an intrauterine sac at an earlier gestational age. A gestational sac should always be seen in the patient with a viable IUP when the serum βHCG reaches 2000 mIU/mL. In many cases, the gestational sac can be seen at a level of about 1000 mIU/mL [34]. Ultrasonography is also very helpful in diagnosing blighted ovum or threatened abortions, which may be part of the differential diagnosis. Following serum βHCG titer (which should double every 48 h in a normal, viable pregnancy) has no role in a patient with a suspected ruptured ectopic pregnancy, as that patient needs immediate surgical attention. Depending on the severity of hemorrhage, hemoglobin concentration might be lowered or even normal [35]. Misleading and unexpected laboratory values such as hyperglycemia might also be present [36]. Many times, diagnosis of an ectopic pregnancy prior to rupture may not be practical because the patient may not even know she is pregnant. These numerous diagnostic pitfalls are the reason for the maxim that any pregnant patient has an ectopic pregnancy until proven otherwise. All women of childbearing age should have a pregnancy test performed regardless of the date of their last menstrual period. Among women with symptoms and inconclusive ultrasound assessments, the progesterone test (five studies with 1998 participants and cutoff values from 3.2 to 6 ng/mL) predicted a nonviable pregnancy with pooled sensitivity of 74.6%, specificity of 98.4%, positive likelihood ratio of 45 (7.1–289), and negative likelihood ratio of 0.26. The median prevalence of a nonviable pregnancy was 73.2%, and the probability of a nonviable pregnancy was raised to 99.2% if the progesterone was low. For women with symptoms alone, the progesterone test had a higher specificity when a threshold of 10 ng/mL was used and predicted a nonviable pregnancy with pooled sensitivity of 66.5%, specificity of 96.3%, positive likelihood ratio of 18 (7.2–45), and negative likelihood ratio of 0.35. The probability of a nonviable pregnancy was raised from 62.9 to 96.8% [37].

15.1.6.2 Transabdominal Ultrasound

When heterotopic pregnancy is the cause, transabdominal ultrasonography demonstrates free intraperitoneal fluid and a normal-looking intrauterine gestation with a positive fetal heart rate. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of transabdominal ultrasonography as a diagnostic modality in evaluation of suspected ectopic pregnancy were 73.1%, 75%, 95%, 30%, and 73.3%, respectively, while transvaginal ultrasonography was found to have 92.3% sensitivity, 75% specificity, 96% positive predictive value, 60% negative predictive value, and 90% accuracy [38].

> Transvaginal ultrasonography is superior to transabdominal ultrasonography in the evaluation of suspected ectopic pregnancies, so transvaginal ultrasonography is important for the early and accurate diagnosis of ectopic pregnancy.

15.1.6.3 Transvaginal Ultrasound

Positive pregnancy tests in the presence of abdominal pain mandate bedside sonography in the emergency department to locate the position of the fetal sac. The transvaginal technique is preferred because of its increased sensitivity for detecting an IUP and its superior visualization of the adnexa [3]. Most patients with ectopic pregnancies have some abnormality on the sonographic scan [39]. These abnormal findings include a cystic or complex adnexal mass (60–90%) and free fluid in the peritoneal cavity (25–35%, higher in a ruptured ectopic pregnancy) and should raise the suspicion of ectopic pregnancy. However, the findings are nonspecific, and not visualizing an ectopic pregnancy on ultrasonography can never definitely exclude it as a possible diagnosis. Location of ectopic fetal heart activity points to a clear diagnosis of ectopic gestation [27]. There are pitfalls involved with overreliance on laboratory values in the evaluation of ectopic pregnancy. Serum βHCG that is above the "discriminatory" level (at which ultrasound should be able to detect an IUP) might lead to a diagnosis of ectopic pregnancy when no IUP is visualized; however, values that fall below this level do not obviate the need for an emergent ultrasound. In many cases, ultrasound might nonetheless be diagnostic. Recently, a case was diagnosed with three-dimensional sonography [39].

Since ectopic pregnancies are normally discovered and removed very early in the pregnancy, an ultrasound may not find the additional pregnancy inside the uterus. When βHCG levels continue to rise after the removal of the ectopic pregnancy, there is the chance that a pregnancy inside the uterus is still viable. This is normally discovered through an ultrasound.

The following guidelines were laid down for ultrasound diagnosis of an *ectopic pregnancy within a Cesarean scar* [40]: (1) an empty uterine cavity and cervical canal, (2) development of the gestational sac in the anterior portion of the lower uterine segment, and (3) the absence of a healthy myometrium between the bladder and the gestational sac.

Intrauterine gestation with hemorrhagic corpus luteum can simulate heterotopic/ectopic gestation both clinically and on ultrasound [41]. Other surgical conditions of the acute abdomen can also simulate heterotopic gestation clinically and hence the difficulty in clinical diagnosis. Bicornuate uterus with gestation in both cavities may also simulate a heterotopic pregnancy. High-resolution transvaginal ultrasound with color Doppler will be helpful as the trophoblastic tissue in the adnexa in a case of heterotopic pregnancy shows increased flow with significantly reduced resistance index [12].

15.1.6.4 Abdominal CT

Ectopic pregnancy commonly presents as a ring-enhancing adnexal cystic mass surrounded by hemoperitoneum on abdominal CT (Fig. 15.3).

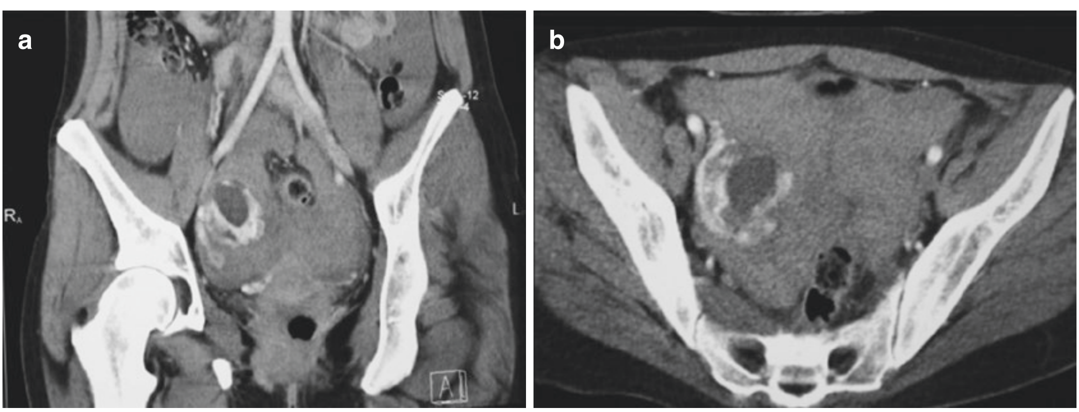


Fig. 15.3 (**a**) A coronal multiplanar reconstruction and (**b**) axial CT with i.v. contrast showing a solid-cystic abnormal mass measuring 45 × 40 mm, well vascularized, with a strong and early peripheral contrast enhancement in the right adnexal area. Reproduced with permission from [42]

15.1.6.5 Abdominal MRI

It is important to distinguish among cervical pregnancy, cervical abortion, and uterine scar pregnancy. If 3D ultrasound is not available, MRI is used to confirm the diagnosis of cervical pregnancy, as tissue characterization is better with MRI (Fig. 15.4) when compared with ultrasound, especially in doubtful cases [43]. The MRI findings of cervical pregnancy include [43] (1) the presence of a mass with heterogeneous signal intensity and (2) partial or complete dark rim on T2-weighted images.

15.1.6.6 Culdocentesis

Culdocentesis may be performed to gain additional information. A needle is inserted through the vaginal wall into the posterior cul-de-sac with possible findings:

- A dry tap is inconclusive
- A few cubic centimeters of clear fluid (peritoneal fluid) rules out a ruptured ectopic, but neither rules out an unruptured ectopic
- A lightly bloody fluid (hematocrit <15) is inconclusive. This could be from a traumatic tap, or early, mild bleeding from an ectopic
- Moderately bloody fluid (hematocrit >15) indicates hemoperitoneum consistent with ruptured ectopic but is nonspecific, and any internal bleeding (hemorrhagic ovarian cyst) can give this result
- Bright red, clotting blood usually indicates a traumatic tap or aspiration of blood from a vessel

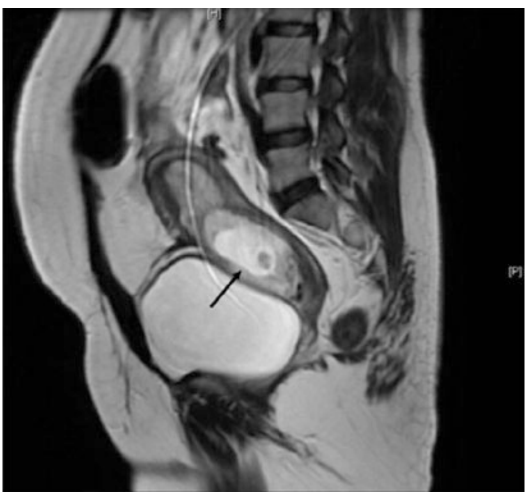


Fig. 15.4 A coronal multiplanar T2-weighted MRI sagittal section of the pelvis showing a gestational sac with fetal pole in the closed cervix (*arrow*) and hour-glass configuration of the uterus with thickened endometrium. Reproduced with permission from [44]

Today, it is rarely done because it is not specific and is invasive, and with the use of abdominal CT scan, it's lost its significance. Only about 50% of patients with a positive culdocentesis have a ruptured Fallopian tube [45].

15.1.6.7 Diagnostic Laparoscopy/Laparotomy

Ectopic pregnancy is commonly diagnosed during exploration (Fig. 15.5); primary ovarian pregnancy is usually diagnosed only at operation, although it may resemble a hemorrhagic corpus luteum (Fig. 15.6). Laparoscopy in the diagnosis of ectopic pregnancy was suggested in 1937 by Hope in the

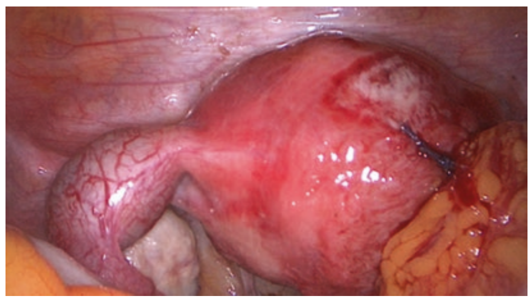


Fig. 15.5 Laparoscopic view of a 30 × 20 mm unruptured left ampullary pregnancy. The intermediate portion of the Fallopian tube can clearly be seen to be distended and blue. Reproduced from [48] under the CC BY 4.0

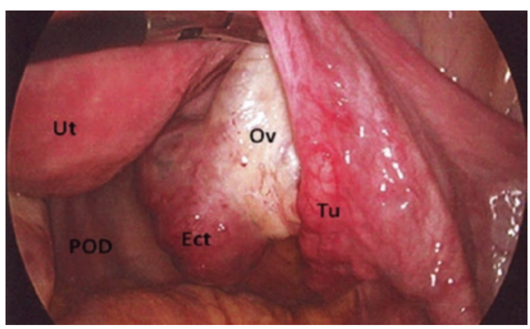


Fig. 15.6 Laparoscopic view of an unruptured right ovarian pregnancy. *Ut* uterus, *POD* pouch of Douglas, *Ect* ectopic pregnancy, *Ov* right ovary, *Tu* Fallopian tube. Reproduced from [49] under the CC BY 3.0

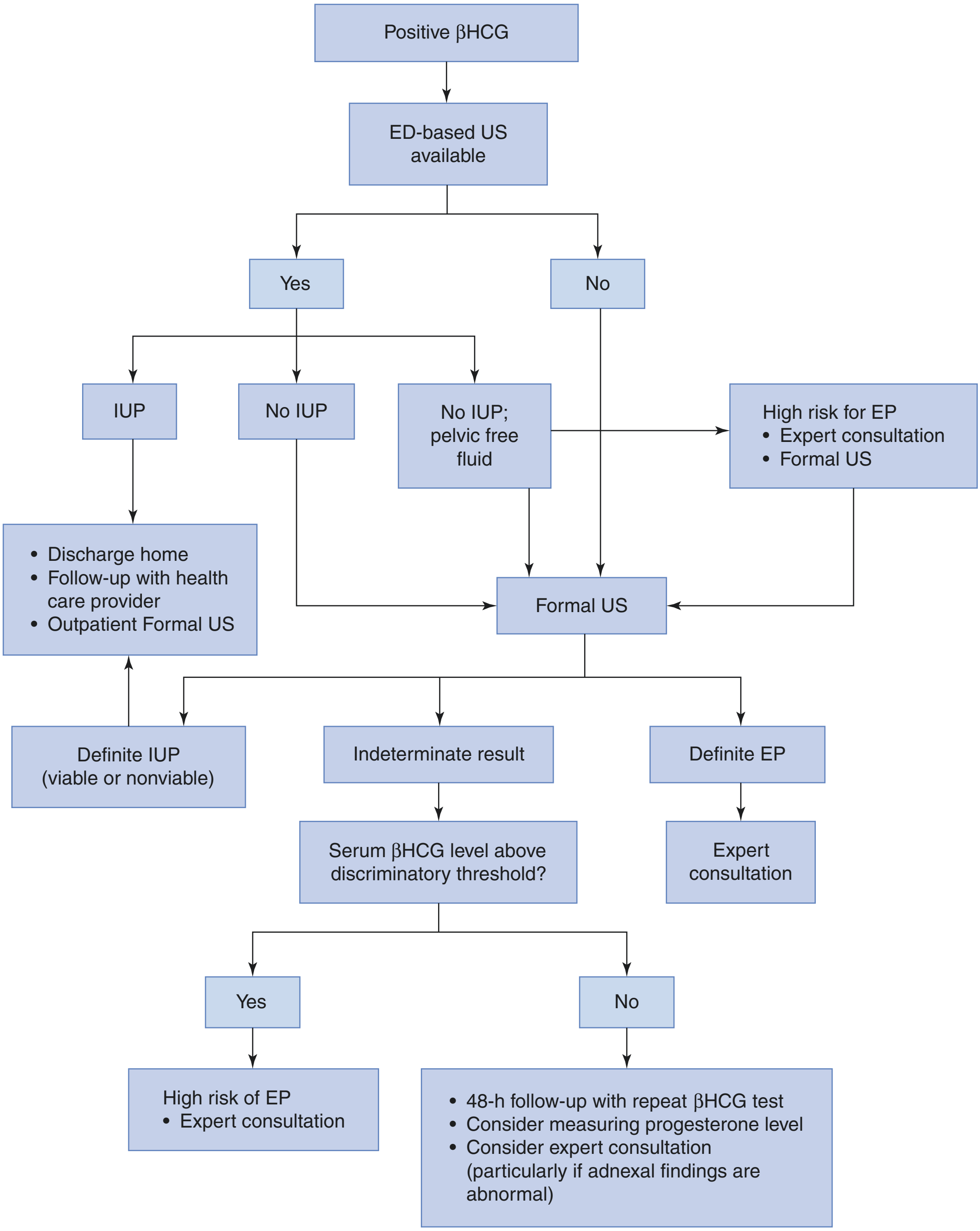


Fig. 15.7 Recommended approach to investigating first-trimester pain or bleeding in the hemodynamically stable patient in the emergency department (*ED*). βHCG β-human chorionic gonadotropin, *US* ultrasonography, *IUP* intrauterine pregnancy, *EP* ectopic pregnancy. Reproduced with permission from [5]

United States [46]. Unfortunately, a correct diagnosis at the time of surgery could be made in only 28%, because it was difficult to distinguish an ovarian pregnancy from a hemorrhagic corpus luteal cyst intraoperatively [47]. Figure 15.7 shows one of the recommended approaches to investigating first-trimester pain or bleeding in the hemodynamically stable patient in the emergency department.

15.1.7 Treatment

When the diagnosis of ectopic pregnancy can be neither established nor excluded by complete diagnostic workup, management depends upon many factors. The overall condition and stability of the patient, the availability of close follow-up care with an obstetrician/gynecologist, and the proximity of the patient to the hospital are important considerations if the discharge is being contemplated. Decisions regarding the disposition of such patients should be made with a consulting obstetrician/gynecologist, and in some cases, admission to the hospital or surgical exploration might be preferred options.

15.1.7.1 Historical Perspective

In 1849, Harbert of Louisville was the first to perform surgery early enough to stop fatal bleeding [50]. Robert Lawson Tait in London, after having performed autopsies on several women, recognized that appropriate dissection and ligation of bleeding vessels would be effective in the treatment of ectopic pregnancy. He successfully performed a laparotomy to ligate the broad ligament and removed a ruptured tube. By 1885, Tait had accumulated a relatively large number of successful cases of salpingectomies [51, 52].

It is interesting that Ralph Waldo, in 1910, at the meeting of *American Association of Obstetricians and Gynecologists* presented the results at Lebanon Hospital of the deferred operation for extrauterine pregnancy. His study was based on an analysis of 81 cases, about 70%, of which were brought into the hospital in profound shock. None of the patients were operated unless they showed signs of recovery from the shock which followed the hemorrhage. It was argued by the author that a woman suffering from a ruptured ectopic pregnancy seldom, if ever, dies of the hemorrhage but of the shock which usually follows the hemorrhage, and if the patient is subjected to the additional shock of the operation, the chances of recovery are minimized. This contention was supported by many others. Robb proved experimentally that a hemorrhage will cease in from 15 to 20 min. He also maintained that a woman who weighs 130 pounds must lose 4 pounds of blood before she will succumb from the effects of the hemorrhage, and so large an amount of blood is rarely found in the free abdominal cavity during an operation or postmortem examination. Robb further contends that the sudden removal of a large quantity of recently accumulated fluid in the abdominal cavity, before the vessels have had time to adapt themselves to the altered mechanical conditions, is dangerous and may be followed by syncope. He maintained that patients in whom the bleeding wound is sufficient to cause death are rarely seen in time to be saved by the operation, and so long as there is reasonable evidence that an immediate operation may be the wrong procedure, it is our duty to hold our hands and leave something to nature [53]. At that time, there were two distinct schools—one advocating the immediate operation and the other the deferred operation—for ruptured extrauterine pregnancy.

In 1913, it is stated in Hartmann's textbook that "every ectopic when diagnosed should be operated upon." Expectant management led in 86% of women to death, but surgery saved 85% of women [54]. The introduction of asepsis, anesthesia, antibiotics, blood transfusions, and methotrexate saved the lives of many women with ectopic pregnancy and eliminate the need for the operation in the selected group of patients.

15.1.7.2 Fallopian Tube Pregnancy

Fallopian Tube-Sparing Surgery

Tube-sparing surgery is accomplished by removal of the ectopic pregnancy from the Fallopian tube via linear salpingostomy by making an incision on the antimesenteric portion of the tube over the bulge of the ectopic pregnancy, removing the pregnancy, achieving hemostasis, and allowing the tube to heal by secondary intention. There are no differences in subsequent spontaneous pregnancy rates, adhesion formations, or fistula formation with or without closure of the incision site [55, 56] but leads more often to recurrent ipsilateral ectopic pregnancy site, hemorrhage, and persistent trophoblastic tissue [57]. Trophoblastic tissue persists in approximately 5% of patients [58].

All patients must undergo follow-up βHCG levels.

A fimbrial expression consists of "milking" the pregnancy out of the tube. This technique probably should be reserved for ectopic pregnancies located at or very near the fimbria itself.

For *unruptured* tubal pregnancy, conservative therapies with methotrexate or laparoscopic salpingostomy are currently the methods of the first choice that can prevent serious complications in subsequent gestations [59]. Ovarian reserve and subsequent ART cycle outcomes (without a time-dependent effect) were reassuring after methotrexate for unruptured ectopic pregnancy. No adverse impact of methotrexate was detected in the large fertility cohort [60].

Salpingectomy

Salpingectomy is the procedure of choice if the woman has no desire for further pregnancies. It also may be necessary for hemostatic control of an attempted conservative approach with salpingostomy or with a tube that appears unable to be salvaged. Salpingectomy is the standard procedure in a patient who is hemodynamically unstable. It has also been suggested that women with a history of infertility may be better served with salpingectomy; as it has been shown in that subset of patients, treatment with salpingectomy resulted in equivalent pregnancy rates and a decrease in recurrent ectopic pregnancy [61].

Hemodynamically Unstable Patient

A patient who is hemodynamically unstable requires emergency laparotomy for surgical treatment. Laparoscopy and medical therapy (i.e., methotrexate) have no role. Patients who have a diagnosis or suspected diagnosis of ruptured ectopic pregnancy might require vigorous and immediate resuscitation with fluids and blood products before surgical intervention. Oxygen should be applied, and an emergent obstetric consultation should be obtained. In a stable patient who does not have suspected rupture, nonoperative management with methotrexate therapy and close follow-up care might be considered in consultation with the obstetrician/gynecologist [3].

Laparoscopy

During the 1970s and 1980s, laparotomy was gradually replaced by operative laparoscopic options. Numerous first-trimester pregnancies have been exposed to laparoscopy to "rule out ectopic pregnancy" and progressed to normal-term gestations [62]. This experience created the rationale for reconsidering the selected use of laparoscopic surgery in pregnant women with gallstone disease who were obviously not candidates for medical management, who failed medical management, or who had suspected appendicitis.

Shapiro and Adler [63] reported laparoscopic salpingectomy using electrocoagulation followed by excision for an ectopic pregnancy in 1973. Salpingotomy by laparoscopy was first reported using multiple punctures in 1980 [64]. Linear salpingotomy with a cutting current was published by DeCherney et al. in 1982 [65]. If clinically possible, the patient is better served with a laparoscopic approach with reduced morbidity, recovery time, costs, and equivalent future fertility rates compared with laparotomy [66, 67].

Whether laparoscopic treatment should be performed conservatively (salpingotomy) or radically (salpingectomy) in women wishing to preserve their reproductive capacity has long been the subject of debate. The result of a randomized controlled trial on salpingotomy versus salpingectomy without contralateral tubal pathology showed that salpingotomy does not improve time to spontaneous ongoing pregnancy and leads more often to persistent trophoblast [57].

> In women with a desire for future pregnancy and with a tubal ectopic pregnancy in a solitary tube or in the presence of contralateral tubal pathology, (laparoscopic) salpingotomy is the treatment of choice [68, 69].

In case salpingectomy is performed due to a failed salpingotomy or other surgical difficulties, IVF is the appropriate treatment option for the loss of fertility. It should be remembered that approximately 3% of ectopic pregnancies are not visualized by laparoscopy. Typically, these are very early gestations. If a pregnancy has been previously determined to be nonviable by serum βHCG or if it is an undesired pregnancy, endometrial sampling by suction curettage may be performed to determine whether an IUP is present. If chorionic villi are obtained from the uterine cavity, the presence of a concurrent

ectopic pregnancy along with the intrauterine one is highly unlikely. The reported incidence of coexistent pregnancies in the general population (i.e., intrauterine and extrauterine) is between 1/4000 and 1/30,000 [66, 70]. Sampling the endometrium with biopsy instruments does not obtain an adequate sample for diagnosis and should not be used.

15.1.7.3 Ovarian Pregnancy

The state of the concerned ovary dictates further treatment. If the remaining ovary looks normal, then a dissection and resection of the gestational sac are performed (Fig. 15.8). In some cases where the ovary is much altered, total oophorectomy may be done. Antimitotic drugs like methotrexate are added when the decrease of the level of βHCG is not sufficient [7].

15.1.7.4 Cervical Pregnancy

In clinically stable patients, if ultrasound measurements show no cardiac activity and the gestational period is less than 9 weeks, systemic methotrexate may be tried [72]. Gestational period more than 9 weeks with the presence of cardiac activity demonstrated on ultrasound in a clinically stable patient may require the addition of intra-amniotic potassium chloride in addition to systemic methotrexate [72]. Second- or third-trimester diagnosis may warrant hysterectomy. In a hemorrhaging patient, the treatment options are tamponade with Foley balloon, large vessel ligation, or angiographic embolization with hysterectomy reserved for intractable bleeding [72]. Often, more than one method is usually tried in the termination of cervical pregnancy [72].

15.1.7.5 (Incidental) Appendectomy

See Chap. 1.

15.1.7.6 Anesthetic and Perioperative Management

See Chap. 21.

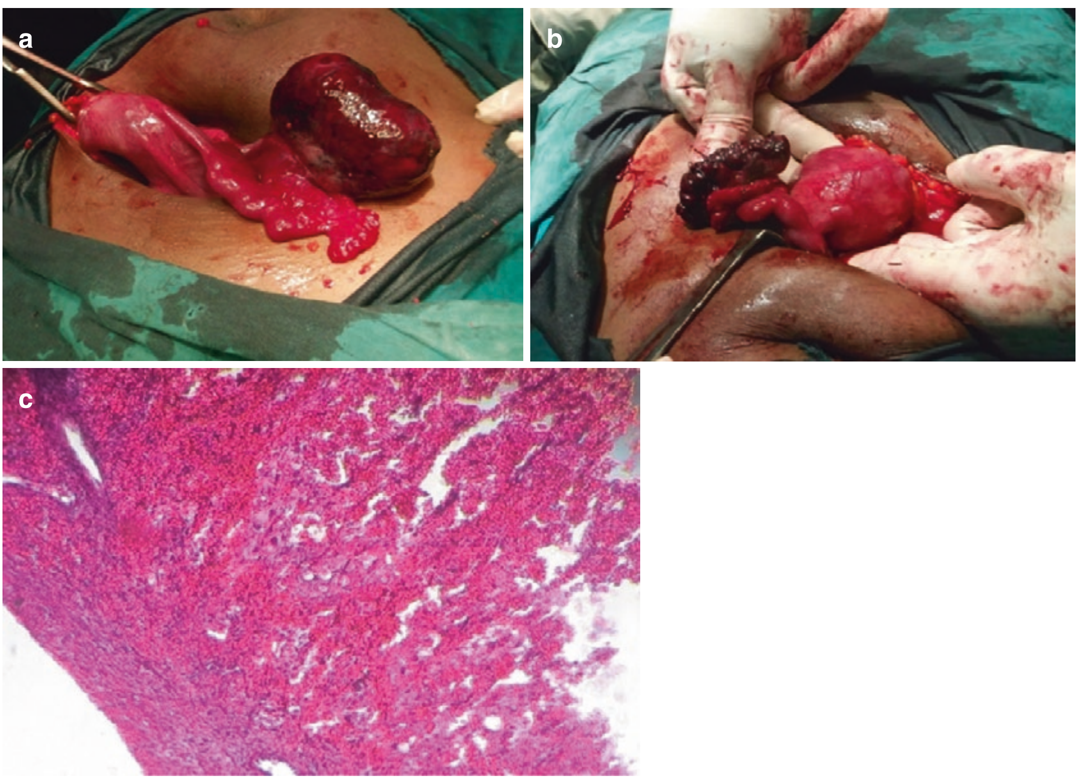


Fig. 15.8 (**a**) Intraoperative photograph showing normal uterus, the left round ligament, the left Fallopian tube, and the ovary containing the gestational sac. (**b**) An operative aspect of the left ovary after resection and ablation of the gestational sac and hemostatic suture. (**c**) Micrograph of the specimen of ovarian resection under hematoxylin–eosin stain showing decidual cells, trophoblastic elements, and the ovarian capsule. Reproduced from [71] under the CC BY 2.0

15.1.7.7 Prevention and Treatment of Preterm Labor

See Chap. 23.

15.1.8 Prognosis

While the number of ectopic pregnancies has increased, the death rate from this disorder has steadily declined. The mortality rate in 1952 in the United States was 2.4% [73]. Still, the maternal mortality rate in the United States ranged 200–400/10,000 cases of ectopic pregnancies and accounts for 13% of all pregnancy-related deaths [2]. The decreased mortality rate is secondary to the effects of early detection and intervention. With the advent of conservative surgery, the emphasis on early diagnosis and increased awareness of this condition may be an important factor in further reducing the morbidity and mortality of ectopic pregnancy.

Mortality of a tubal pregnancy at the isthmus or within the uterus (interstitial pregnancy) is higher as there is increased vascularity that may result more likely in sudden major internal hemorrhage.

The survival rate of the uterine fetus of an ectopic pregnancy is around 70%. Successful pregnancies have been reported from ruptured tubal pregnancy continuing by the placenta implanting on abdominal organs or on the outside of the uterus.

15.2 Ruptured Cornual Pregnancy

15.2.1 Definition

Rudimentary horn of a unicornuate uterus arises as a result of a partial development of one uterine horn and incomplete fusion of the two Müllerian ducts. In more than 75% of cases of the unicornuate uterus, a contralateral rudimentary horn is present. The majority of rudimentary horns contain functional endometrium and do not communicate with the unicornuate uterus [74–76]. However, the rudimentary horn has been described in the literature under various terms, including *unicornuate uterus with rudimentary horn*, *uterus bicornis unicollis with rudimentary horn*, *uterus bicornis unicollis with atretic horn*, *uterus bicornis with accessory horn*, *Roberts' uterus*, and *hernia uterus inguinale*. This freedom of terminology makes an assessment of this condition more difficult.

Contrary to the American Fertility Society classification of uterine anomalies, rudimentary horns may occur without a corresponding unicornuate uterus. In the bicornuate uterus, if pregnancy occurs in the well-developed horn, it continues normally, and only in cases where conception occurs in the rudimentary horn, there is significantly increased the risk of uterine rupture [77], while others claim that all rudimentary horn pregnancies rupture [74]. The first case of rudimentary horn rupture was reported in 1669 by Francois Mauriceau [78].

15.2.2 Incidence and Pathophysiology

Noncommunicating horns account for 70–92% of cases [74–76]. Pregnancy in a noncommunicating rudimentary horn has a reported incidence of 1/76,000–1/150,000 [74, 79], with more than 600 cases published [74–76, 80, 81]. Of all ruptures, 13% occur in the first, 67% in the second, and 20% in the third trimester [74]. There is no significant difference in rupture rates of communicating and noncommunicating horns (52% and 47%, respectively). Since 1900, 30% of pregnancies went to term, but from 1990 to 1999, this was reduced to 6% because of earlier detection and intervention [74]. Rupture of uterine horn occurs because of the inability of the malformed uterus to expand with increasing gestational age. It occurs following the transperitoneal migration of sperm or of fertilized ovum zygote [76]. Pregnancy in a rudimentary horn can result in the rupture between 10 and 20 weeks of gestation with associated life-threatening hemorrhage [82] due to poorly developed musculature that cannot stretch. It is extremely uncommon for such cases to result in a viable fetus as they often result in rupture of the horn before the third trimester [83]. Only 10% cases reach term, and the fetal salvage rate is only 2% [84, 85]. Rupture occurs commonly because of underdevelopment, variable thickness, and poor distensibility of myometrium and dysfunctional endometrium. Rudimentary horn pregnancy can be further complicated by placenta percreta due to the poorly developed musculature, scant decidualization, and small

size of the horn, the reported incidence being 11.9% [86, 87], or by twin pregnancy [86].

For pregnancies that implant in a rudimentary horn of a uterus, a particularly high risk of rupture (≤81%) is associated with the induction of labor [88]. This phenomenon was first observed by Whitehouse in 1912 (Fig. 15.9) [77]. The decision for induction of labor in women with a congenitally anomalous uterus, especially in cases of a previous CS, must be carefully considered and given the higher incidence of UR reported. Although the UR rate for unscarred anomalous uteri during pregnancy is increased relative to that for normal uteri, the precise increase in risk associated with the different types of uterine malformations remains uncertain.

15.2.3 Clinical Presentation

As rudimentary horn pregnancies are always associated with catastrophic outcome, every effort should be made to diagnose them before pregnancy or at an early gestation. A detailed history should be taken during the first visit including any complaints of severe dysmenorrhea. However, the rudimentary horn may be underdeveloped and its endometrium may be nonfunctional and dysmenorrhea may be absent in 50% of cases [75, 83]. The incidence of endometriosis in functional rudimentary horns is similar to the incidence in women with normal uteri (<15%) [74]. It is important to keep an index of suspicion in high-risk groups. Müllerian anomalies are commonly associated with spinal and cloacal and renal anomalies (45–60%) [89–92]. The particular association of unilateral renal agenesis or ectopia, uterine duplication or unicornis, and vaginal agenesis has been well described [93]. Unilateral renal agenesis is a useful predictor of an ipsilateral obstructive Müllerian anomaly 55–70% of the time [94], but the reverse is not true. Significant rate (29–44%) of rudimentary horns were associated with abnormal renal anatomy [75]. The unicornuate uterus with a rudimentary horn may be associated with complications such as hematometra, endometriosis, infertility, recurrent miscarriages, preterm labor, malpresentation, and placenta accreta [95]. A possible explanation of complications is that the horn is noncommunicating in approximately 70–90% of cases, and fertilization is thought to take place by transperitoneal migration of gametes or occurs in the pouch of Douglas. The most common reasons for hospitalization in women who were found later to have rudimentary horns were an ectopic pregnancy (25%), chronic pelvic pain (20%), pelvic tumor (20%), and primary infertility (15%) [92].

A careful pelvic examination showing deviated uterus with a palpable adnexal mass causing deviation of the uterus and cervix to one side [96, 97], or a bicornuate uterus with the horns a wide distance apart, should arouse suspicion of a Müllerian anomaly.

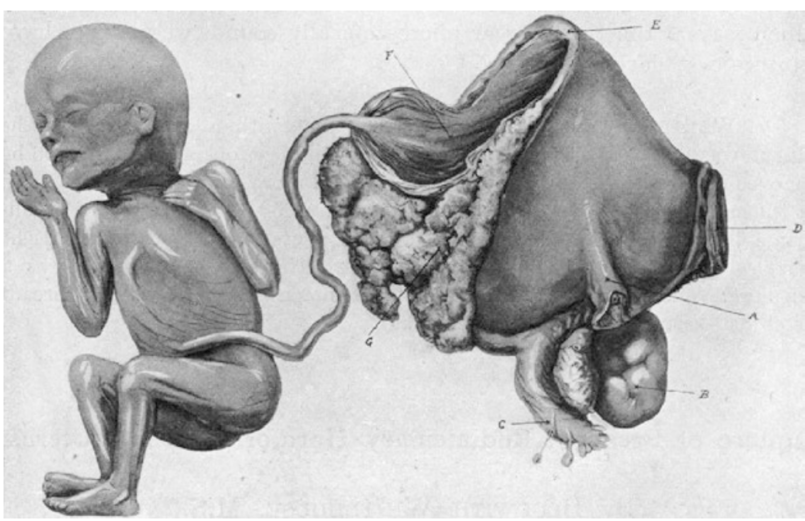


Fig. 15.9 Ruptured four and a half months of gestation in the rudimentary corn of a uterus bicornis. (*A*) Round ligament; (*B*) ovary; (*C*) Fallopian tube; (*D*) section through point of attachment of rudimentary corn with the remaining uterine horn; (*E*) rupture in wall of corn through which fetus escaped into peritoneal cavity; (*F*) amniotic cavity; (*G*) placenta. Reproduced with permission from [77]

15.2.4 Diagnosis

There is persistently low preclinical and preoperative detection of rudimentary horn presentations (14% overall) [74]. The preclinical detection rate for obstetric presentations is only 8%, which has not changed much from reports of 5–6% since the 1960s [76, 92]. Diagnostic criteria for pregnancy in a rudimentary horn have subsequently been described such as [98]:

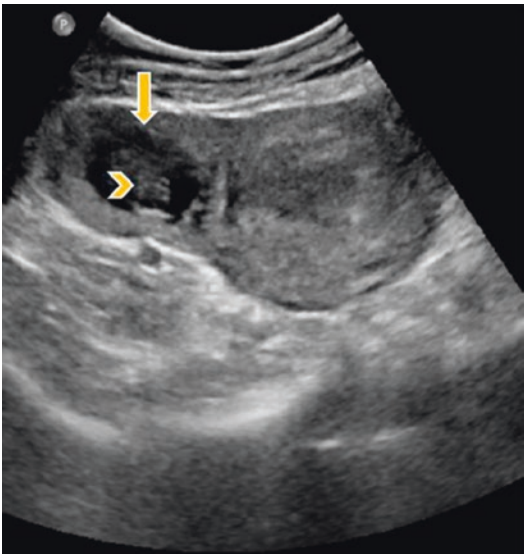


Fig. 15.10 Ultrasound at the seventh week of pregnancy shows bicornuate uterus with a gestational sac in the smaller right horn (*arrow*). Fetal pole is seen within the sac (*arrowhead*). Reproduced with permission from [104]

- Detection of a single interstitial tube in an empty uterus adjacent to the pregnancy
- Free mobility and the presence of a vascular pedicle adjoining the gestational sac and the lateral aspect of the empty uterus

15.2.4.1 Abdominal Ultrasound

The sensitivity of ultrasound diagnosis of pregnancy in a rudimentary horn is around 30% [99, 100] with the first case of cornual pregnancy diagnosed on ultrasound in 1983 [101]. Previously stated criteria can be used with relative ease in the first trimester (Fig. 15.10), but as pregnancy progresses, it becomes more difficult to diagnose pregnancy in the rudimentary horn [102]. Furthermore, it is difficult to demonstrate the subtle anomalies that may be associated with this condition. Three-dimensional ultrasound may also play a useful role in evaluating uterine anomalies [98, 99, 102]. Even heterotopic corneal pregnancy (Fig. 15.11) can be detected with transvaginal ultrasound [103].

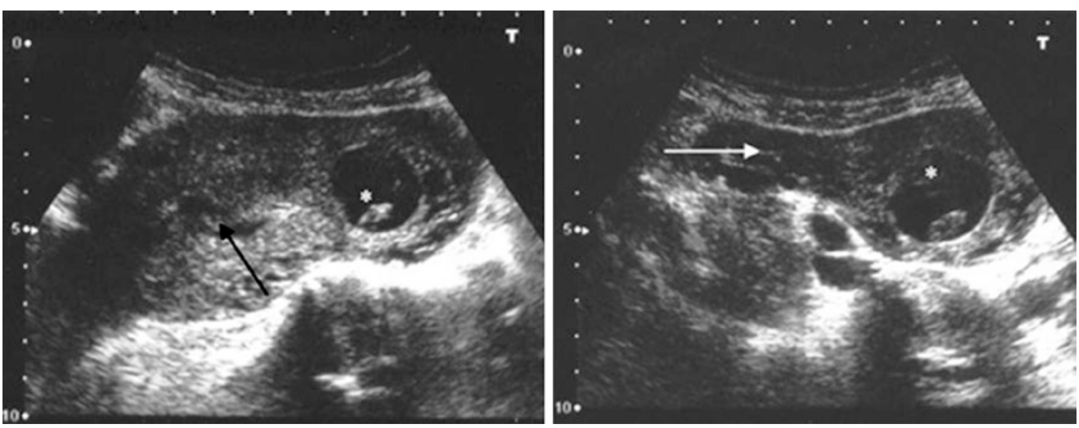


Fig. 15.11 The image in the left panel shows an intrauterine gestation (*black arrow*) coexisting with an ectopic cornual pregnancy (*asterisk*) with a sac of 25 mm in diameter, containing an embryo with a crown rump length of 13 mm. The image in the right panel shows the ectopic pregnancy (*asterisk*) located in the right cornual region in continuity with the uterine cavity, in a funnel-shaped area in the upper uterine body that receives the insertion of the right Fallopian tube (*white arrow*). Reproduced from [103] under the CC BY 3.0

15.2.4.2 Hysterosalpingography

Hysterosalpingography can miss a noncommunicating uterine horn [105]. Diagnostic hysteroscopy may indicate a major midline malformation if tubal ostia are absent [106], although the procedure often needs to be done in conjunction with laparoscopy and dye studies. A high level of agreement between 3D ultrasound, hysterosalpingography, and laparoscopy in the classification of uterine morphology has been reported [107, 108]. The enlarging horn with thinned myometrium can obscure the adjacent anatomic structures, and the sensitivity further decreases as the gestation increases.

15.2.4.3 Abdominal CT

If abdominal and/or vaginal ultrasound is equivocal and the patient stable, abdominal CT or MRI is indicated. CT is performed if the patient is hemodynamically stable and MRI is not available. Free peritoneal fluid and the location of corneal pregnancy can be visualized (Fig. 15.12).

Fig. 15.12 Abdominal CT (coronal section) shows gravid uterus at the seventh week of pregnancy with gestational sac toward the right side (*arrow*). Moderate amount of free fluid in the abdomen especially around the liver (*arrow head*). Reproduced with permission from [104]

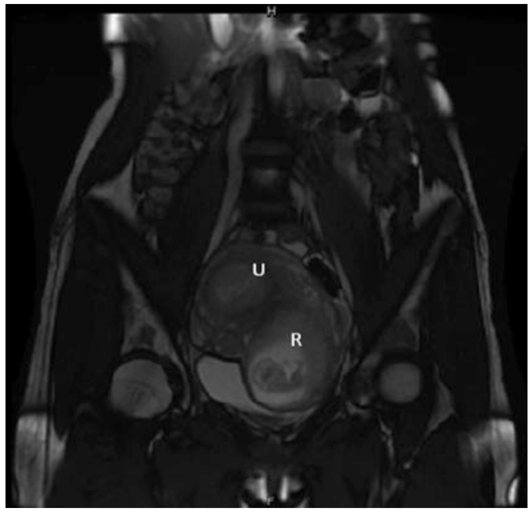


Fig. 15.13 Abdominal MRI (T2 coronal view) showing the uterus (*U*) and the left rudimentary horn (*R*) pregnancy. Reproduced with permission from [80]

15.2.4.4 Abdominal MRI

MRI has proven to be a very useful tool for the diagnosis of pregnancy with a Müllerian anomaly and to confirm the presence of placenta percreta [109]. MRI can define a didelphys uterus with a fetus in one of the uterine bodies (Fig. 15.13). Even with abdominal MRI, the placental invasion could remain elusive and is diagnosed only at laparotomy [83]. Intraoperatively, an extrauterine pregnancy with a well-defined placenta differentiates a rudimentary horn pregnancy from an abdominal pregnancy because the placenta fits into the confines of the horn.

15.2.5 Treatment

15.2.5.1 Intra-abdominal Approach

Traditionally laparotomy has been the approach of choice, but with increasing expertize in laparoscopic surgery, there is an increasing number of laparoscopic treatment of rudimentary horn pregnancy [110–112]. Laparoscopy, though the gold standard for surgical management of hemodynamically stable women with ectopic pregnancy, had long been considered a contraindication in women with hypovolemic shock. This is because of the effect of pneumoperitoneum, the positioning

of the patient, and the duration of surgery. There is always a special concern of pressure on the diaphragm and stomach posing a significant threat of resuscitation and aspiration and pressure on the blood vessels which results in reduced cardiac output (see Chaps. 21 and 22). Most of the second-trimester rudimentary horn pregnancies have been managed by laparotomy [74, 76, 82, 113–115] with some exceptions [116]. One of the reasons is more profuse bleeding from the enlarged uterus with a presentation in hemorrhagic shock. Regardless of the intra-abdominal access the fetus and the placenta should be removed.

15.2.5.2 Procedures

Excision of Rudimentary Horn with Ipsilateral Salpingectomy

When diagnosed early, excision of the rudimentary horn with ipsilateral salpingectomy is the recommended surgical treatment and provides the best prognosis. This has been recommended due to a remote possibility of ectopic pregnancy as a result of transperitoneal migration of the embryo [110, 117, 118]. The procedure can be performed via laparotomy (Fig. 15.14), especially if significant bleeding is present or by laparoscopy (Fig. 15.15). Tracking the course of ureter on the side of the horn is important to avoid inadvertent injury. Another important operative tip is instillation of vasopressin (20 IU/mL in a dilution of 1:60 with normal saline) at the site of attachment of the horn aids in hemostasis [116]. The attachment of the horn to the uterus can be divided using either a medial or a lateral approach, depending upon the type of attachment of the horn. A medial to lateral approach is preferred if the horn is attached to the uterus by a fibromuscular band [110]. Here,

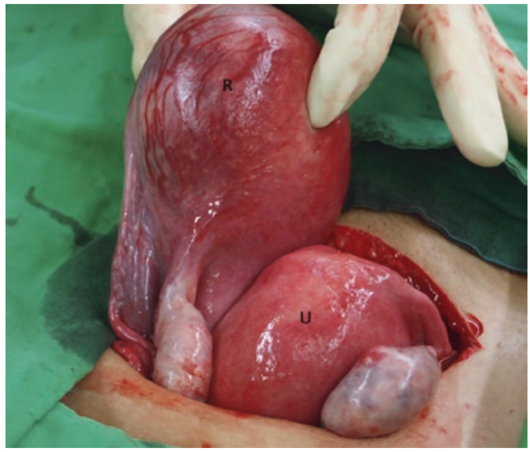


Fig. 15.14 Caudal view of the left noncommunicating horn (*R*) and the uterus (*U*) through Pfannenstiel incision. Reproduced with permission from [80]

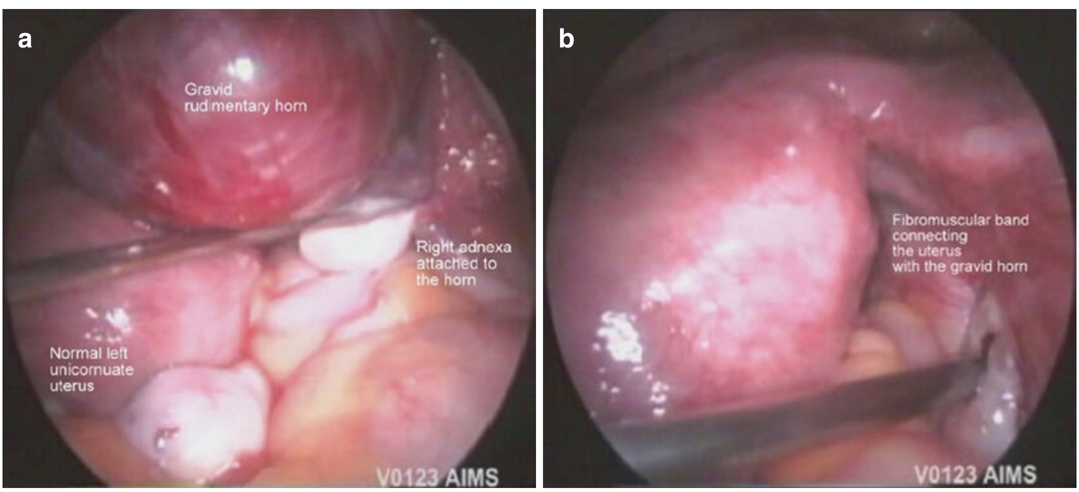


Fig. 15.15 (**a**) Laparoscopic view showing anatomic relationships of the gravid rudimentary horn; (**b**) fibromuscular attachment between the left unicornuate uterus and the pregnant rudimentary horn; (**c**) fibromuscular band being divided; (**d**) lateral attachments of the horn to round ligament; (**e**) tubal attachment divided; (**f**) intact specimen of rudimentary horn pregnancy; (**g**) cut section of resected specimen. Reproduced with permission from [120]

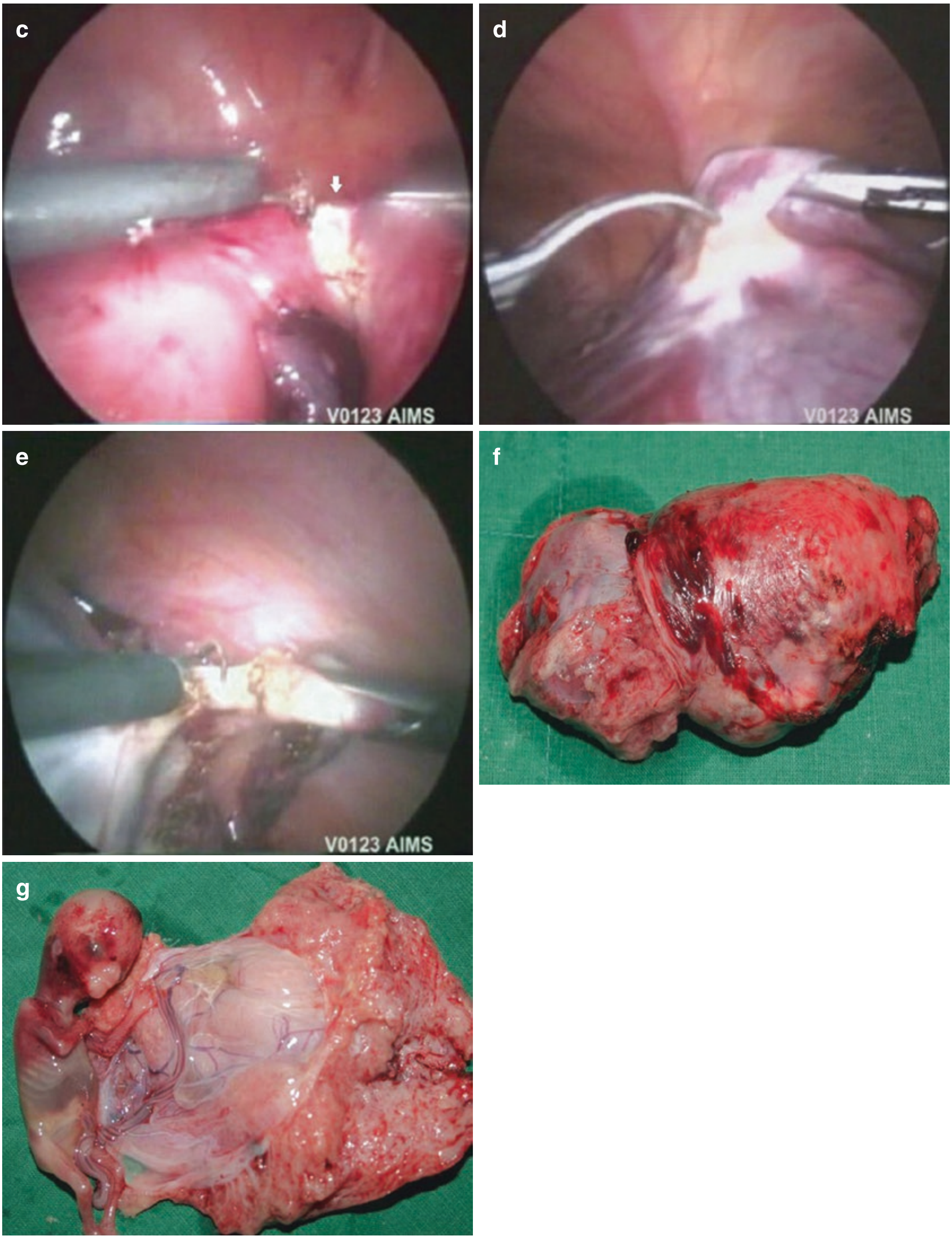


Fig. 15.15 (continued)

the uterine vessel is coursing medial to the horn which is divided early in dissection and hence prevents excessive blood loss during surgery. Lateral to medial approach is utilized if the horn has a broad sessile attachment and the uterine vessel courses lateral to the horn. Electrocoagulation, harmonic scalpel, or stapling device can be used.

Even a spontaneous cornual rupture in the second trimester can undergo a direct repair of a defect closed in two layers with absorbable interrupted intracorporeal mattress sutures [116]. Pregnancy can continue under strict monitoring followed by delivery via elective Cesarean section (CS) [119].

Microsurgical Fallopian Tube Transposition
Microsurgical Fallopian tube transposition of the ipsilateral tube is recommended in the presence of a damaged contralateral tube but in elective settings [121, 122].

15.2.5.3 Anesthetic and Perioperative Management

See Chap. 21. In nonurgent presentations, it is vital to evaluate the type of rudimentary horn and the possible presence of urological anomalies before embarking on the surgical excision, in order to avoid associated complications [110]; hence, the interval excision of the rudimentary horn after the complete preoperative evaluation is recommended [116, 123]. Rudimentary horn carries a risk for associated abnormalities. Therefore, abdominal MRI, after full recovery, should be performed, especially due to high risk of urinary tract anomalies [116].

15.2.5.4 Prevention and Treatment of Preterm Labor

See Chap. 23.

15.2.6 Prognosis

The mortality rate has reduced from 23% at the turn of the twentieth century to 0.5% today probably due to more common and earlier preoperative diagnosis and earlier intervention in ensuing hemorrhage.

15.3 Abdominal Pregnancy

15.3.1 Historical Perspective

The first reference to abdominal pregnancy is found in the Talmud in which rabbis reportedly observed a child which emerged from the abdominal side of the mother. Hindu legend has it that Buddha was born through the right side or armpit of his mother. The first documented report of a successful abdominal pregnancy was in 1500 when a Swiss swinegelder performed abdominal surgery on his wife. Both the mother and child survived. One of the first modern descriptions of the case is by Walker von Solothurn in 1887 [124].

15.3.2 Classification

Abdominal pregnancies can be classified as *primary* when fertilization takes place outside the uterine adnexa or as *secondary* (thought to be more common) which result from undetected rupture of an early tubal pregnancy with subsequent implantation onto the peritoneal surfaces. In very rare cases of uterine rupture (mostly rupture of a unicornuate or bicornuate uterus), the fetus may be extruded into the peritoneal cavity, while the placenta remains functional within the uterus and the gestation continues as an uteroabdominal pregnancy. Primary peritoneal pregnancy can be clinically distinguished from secondary peritoneal pregnancy by *Studdiford's criteria* (see Sect. 9.2.1).

Implantation can occur anywhere in the abdomen including the ligaments, liver, and spleen. Abdominal pregnancy is not strictly defined as *early* before which includes 12–28 weeks of gestation and *advanced* after that period.

15.3.3 Incidence

Hellman and Simon from New York collected 316 reported cases during the period 1809–1935 [125]. They included a series of fetuses from 22 weeks of gestation to term. In 1935, the incidence was 1/9333 pregnancies [126].

The incidence varies widely with geographical location, the degree of antenatal attendance, the level of medical care, socioeconomic status, and even from institution to institution in the same country [127–129]. It is believed that abdominal pregnancy is more common in developing countries probably because of the high frequency of pelvic inflammatory disease in these areas with suboptimal treatment [130, 131]. Heterotopic pregnancy is the coexistence of intrauterine and extrauterine pregnancies. Abdominal pregnancies make up a small percentage of ectopic pregnancies which are a common occurrence [132]. Moreover, 98% of all extrauterine pregnancies are intratubal, 1% is ovarian, and the rest are primary or secondary peritoneal implantations. Atrash et al. estimated in 1987 the incidence of abdominal pregnancy at 10.9/100,000 live births and 9.2/1000 ectopic pregnancies in the United States [129] or between 1/3000 and 1/8000 deliveries in other studies [127, 128, 133, 134]. Ombelet et al. found an incidence of 1/402 pregnancies in developing countries and 1/10,000 pregnancies in developed countries [135]. Advanced abdominal pregnancy is rare and accounts for 1/25,000 pregnancies [136]. Recently estimated rate of occurrence of heterotopic pregnancy is 1/15,000 live births, and the ectopic component is commonly tubal. Its incidence is increased in women undergoing assisted conception with superovulation, IVF-ET, and gamete intrafallopian transfer [137]. The incidence of heterotopic pregnancy has been reported as 1/8000–1/30,000 in natural conception [138]. It may increase as high as 1% with assisted reproductive techniques.

15.3.4 Risk Factors

Risk factors include a history of tubal pregnancies, pelvic inflammatory disease, tubal sterilization, and tubal infertility or tubal reconstructive surgery. Other women at risk include those who conceive despite the use of an intrauterine contraceptive device (IUCD) or progestogen-only contraceptive pills [139]. If none of the above risk factors are present, the undetected rupture of a tubal pregnancy is considered as a case of heterotopic pregnancy. Cocaine abuse has been identified as a risk factor specific for abdominal pregnancy; the associated increase in risk may be up to 20-fold [140]. The first case of abdominal pregnancy after IVF was described in 1988 [141]. Mechanisms discussed for abdominal pregnancy during IVF are [142]:

- Uterine perforation during the transfer
- Spontaneous intra-abdominal fertilization
- Microfistula at the interstitial portion of the uterus

15.3.5 Clinical Presentation

Diagnosis of heterotopic/abdominal pregnancy is a challenge not only for the obstetricians but also for other physicians who are following or treating the patient. Even brilliant surgeons from the first quarter of the twentieth century, such as Berkley, Bonney, Kelly, and Cullen, stated unashamedly that they each have made mistakes in the diagnosis of this condition. In 1936, only 35% were diagnosed correctly before operation [143]. Clinical findings are extremely variable, and even today the preoperative diagnosis is still unsuspected by up to 60% of cases [144]. Sometimes it is found when abdominal exploration is indicated for other causes such as AA or tubo-ovarian abscess [145]. Spontaneous progression of undetected IUP from the time of surgical management of acute or subacute ruptured ectopic pregnancy on postoperative follow-up is rare. On the contrary, spontaneous abortion of an IUP has followed ectopic rupture [146].

Early diagnosis depends on the clinician having a high index of suspicion. Reece et al. defined four common symptoms and findings [146]:

- Abdominal pain
- Adnexal mass
- Peritoneal irritation
- Increase in the size of the uterus

Frequent signs and symptoms include crampy abdominal pain, vaginal spotting or hemorrhage, nausea, vomiting, malaise, and

painful fetal movement [128, 133, 134, 144]. The most common physical findings are abdominal tenderness, an abnormal fetal position, and displacement of the cervix. Tal et al. reported abdominal pain in 83% and abdominal tenderness with hypovolemic shock in 13% of the heterotopic pregnancy cases and vaginal bleeding in half of the patients.

Vaginal bleeding that can be concurrent in ectopic pregnancy is rarely seen in heterotopic pregnancies on account of the intact endometrium of IUP [147]. When the fetus dies, it would cause the cessation of all signs of pregnancy, such as enlargement of the breasts, etc. [148].

Fig. 15.16 Abdominal ultrasound: pregnancy developing outside of the uterus. Reproduced with permission from [152]

15.3.6 Diagnosis

15.3.6.1 Laboratory Findings

Laboratory tests such as abnormally increasing βHCG are not sufficiently reliable on their own to make a diagnosis, as are signs and symptoms such as abdominal pain and tenderness, persistent transverse or oblique lie, and palpable fetal parts [132]. Quantitative measurements of serum βHCG levels are of no use because the IUP will be producing normal and increasing levels of serum βHCG [149]. The absence of uterine contractions during oxytocin challenge testing is highly suggestive of abdominal pregnancy [128].

15.3.6.2 Transabdominal Ultrasound

Transabdominal ultrasound (Figs. 15.16 and 15.17), when coupled with clinical evaluation, has approximately 50–75% success rate [132]. Sonographic findings for the diagnosis of abdominal pregnancy are [150, 151]:

- Demonstration of a fetus in a gestational sac outside the uterus or the depiction of an abdominal or pelvic mass identifiable as the uterus separate from the fetus
- Failure to see a uterine wall between the fetus and urinary bladder
- Recognition of a close approximation of the fetus to the maternal abdominal wall
- Localization of the placenta outside the confines of the uterine cavity

The most frequent and reliable finding was a separation of the uterus from the fetus (90%). Extrauterine placenta (75%) and oligohydramnios (45%) were the next in frequency. Other features such as fetal parts close to the maternal abdominal wall (25%), failure to visualize myometrium between the fetus or placenta and maternal bladder (15%), abnormal fetal lie (25%), poor visualization of the placenta (25%), and maternal bowel gas impending fetal visualization (25%) were noted [151]. To establish the diagnosis, clear identification of the empty uterus as a separate structure is important. This can be accomplished by giving close attention to the lower pelvis to ensure that there is continuity between normally appearing vaginal and endometrial echoes. Also, false-positive diagnoses must be avoided. Findings that mimic abdominal pregnancy include pregnancy in a bicornuate uterus, pedunculated uterine fibroids associated with a gravid uterus, and even an early normal pregnancy in a sharply retroflexed or anteflexed uterus.

15.3.6.3 Abdominal MRI

An MRI scan can also be used to confirm the diagnosis of abdominal pregnancy showing the same characteristics as abdominal ultrasound (Fig. 15.17) with the addition of a more precise definition of the location of the placenta and placental invasion of the surrounding structures (Fig. 15.18).

15.3.7 Treatment

The effort to separate the placenta is attended with great risk of fatal hemorrhage.
Edward Parker Davis, 1904

For the management of abdominal pregnancy, factors such as maternal hemodynamic status, fetal congenital abnormality, fetal viability, gestational age at presentation, and the availability of neonatal facilities should be considered. If the fetus is dead, surgical intervention is generally indicated owing to the risk of infection and disseminated intravascular coagulation. Various clinicians, however, recommend a period of observation of 3–8 weeks to allow atrophy of placental vessels [154]. If the diagnosis is uncertain and ectopic/abdominal pregnancy suspected, laparoscopy can be both diagnostic and therapeutic (Fig. 15.19).

Fig. 15.17 Abdominal pregnancy: live fetus at 17 weeks with normal amniotic fluid. Reproduced with permission from [152]

15.3.7.1 Conservative Treatment

In the management of abdominal pregnancy with an embryo, treatment with methotrexate does not seem to be effective [156], but it could be added to surgical treatment [157]. Preoperative methotrexate treatment minimizes blood loss during surgery and facilitates maximal placental removal in abdominal pregnancy [158]. Because of the risks of placental separation, most advise surgical intervention as soon as the diagnosis of abdominal pregnancy is confirmed, regardless of the fetal condition [130]. However, in some circumstances, it could be possible to await fetal maturity [157].

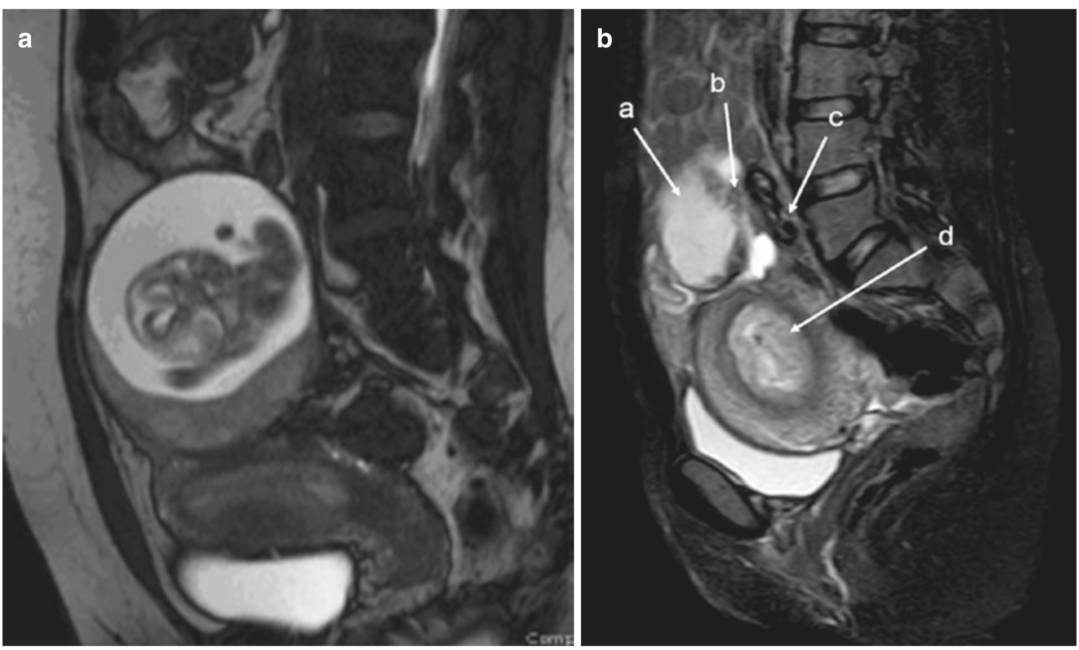


Fig. 15.18 (**a**) MRI showing abdominal pregnancy: placenta is inserted on the posterior wall of the uterus (Reproduced with permission from [153]). (**b**) T2-weighted sagittal MRI of lower abdomen demonstrating the placental invasion. Placenta (*a*), invasion area (*b*), sigmoid colon (*c*), uterine cavity (*d*) (Reproduced from [154] under the CC BY 3.0)

Fig. 15.19 Laparoscopic findings of a reddish and edematous mass on the left infundibulopelvic ligament of early abdominal pregnancy. Reproduced with permission from [155]

>20 Weeks of Gestation

If a conservative approach is to be considered with a diagnosis of abdominal pregnancy at >20 weeks of gestation, the following prerequisites have been proposed [159, 160]:

- The absence of fetal malformation
- The absence of maternal or fetal decompensation
- Continued surveillance of fetal well-being
- Placental implantation low in the abdomen, far away from the liver or spleen
- Adequate amniotic fluid
- Continuous hospitalization in an appropriate facility
- Informed consent from the patient

Maternal surveillance comprises physical examinations, serial ultrasound assessments, measurement of fetal growth, and daily fetal heart rate monitoring. Laparotomy can be planned for 34 weeks of gestation in the absence of complications.

<20 Weeks of Gestation

When the diagnosis is established before 20 weeks, continuing the pregnancy should be exceptional. The importance of informed consent is paramount [157].

15.3.7.2 Surgical Treatment

If the fetus is alive, laparotomy should be performed regardless of gestational age or fetal condition [130, 131]. The reason is mainly based on the unpredictability of placental separation and consequential massive hemorrhage.

Perioperative Embolization

Removal of an abdominal pregnancy by laparoscopy after embolization has been described [161]. Embolization of the placental vascular supply can be performed before surgery to minimize blood loss, during surgery to facilitate maximal placental removal [161–163], and after surgery in case of postoperative hemorrhage [164]. Although no consensus regarding the treatment of the placenta in abdominal pregnancy has been established, most authors advocate leaving the placenta in situ unless the surgeon can be confidently assured that the entire blood supply to the placental bed can be surgically ligated without loss of excessive amounts of blood and the need for extensive blood replacement therapy. Preoperatively, the primary task is to identify all sources of blood supply to the placenta (Fig. 15.20) and to embolize vessels that could be difficult to ligate, such as the hypogastric artery.

Routine angiographic evaluation should include abdominal aortography with renal evaluation, selective celiac and superior mesenteric arteriography, and selective internal iliac arteriography. If embolization is not performed preoperatively, it can be performed postoperatively with the same technique in the presence of persistent bleeding.

Operative Procedure

Laparotomy should be performed through a midline incision [132]. It is advisable to make the incision in the amniotic sac as far as possible from the placental attachment and large enough to extricate the fetus without trauma and to permit the subsequent drainage of amniotic fluid

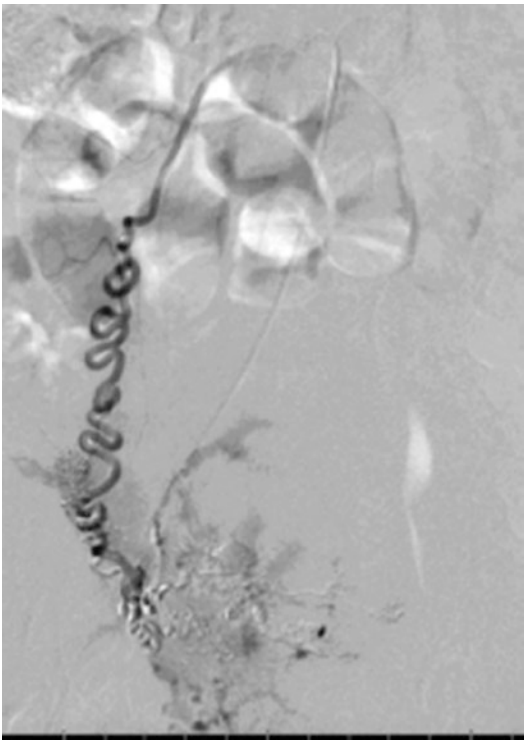


Fig. 15.20 Catheterization of the right ovarian artery, which was supplying the placenta in abdominal pregnancy. Reproduced with permission from [152]

[159]. Because of the high risk of hemorrhage, it is preferable to leave the placenta in place by ligating the umbilical cord at its base. There is no effective method of controlling bleeding in the placental bed by clamping or cautery. Prolonged pressure, hot packs, and topical thrombin-containing compresses have been used with variable success. Use of temporary aortic compression or an abdominal balloon pressure pack in the pelvis can be lifesaving [159]. All efforts should be made to avoid leaving a drainage tube in place, as this increases the risk of abscess formation and septicemia [165]. Nevertheless, it is ideal to remove the placenta if its blood supply can be secured, if the diagnosis is made early in pregnancy, or in cases with the fetal demise of more than 4 weeks' duration [166]. In these circumstances, removing the placenta has been followed by fewer complications, less need for repeat surgery, and fewer repeat hospitalizations [167, 168]. In fact, placental removal has been associated with low morbidity but high mortality

Fig. 15.21 Fetus and placenta attached to the sigmoid colon (see Fig. 15.18b). Reproduced from [153] under the CC BY 3.0

[169]. The actual procedure consists of an initial ligation of the placental blood supply and, afterward, the removal because massive life-threatening bleeding can occur due to the absence of a contracting uterus, which generally would occlude the placental bed [170]. There are also other treatment options regarding the placenta, like partial removal or leaving the placenta in situ. In the case of a partial removal of the placenta, a complete blood supply ligation is needed; if not, massive uncontrollable hemorrhage may occur [156]. Leaving the placenta in situ with the ligation of the umbilical cord can be associated with expectant management or other measures, which can accelerate placental trophoblast involution like methotrexate therapy or embolization [144, 162]. If the placenta is not removed completely, it has been estimated that the remnant can remain functional for approximately 50 days after the operation, and total regression of placental function is usually complete within 4 months [171].

Delay has been advised by some to allow the fetus to die and the placenta to become partly separated. When the fetus has been removed and the placenta found to be firmly attached to the bowel (Fig. 15.21), it is suggested that the membranes be stitched to the abdominal wall and the placenta allowed to remain, while the amniotic sac is packed with sterile gauze. The pressure preventing hemorrhage, the placenta becomes gradually loosened, sometimes piecemeal and sometimes almost entirely.

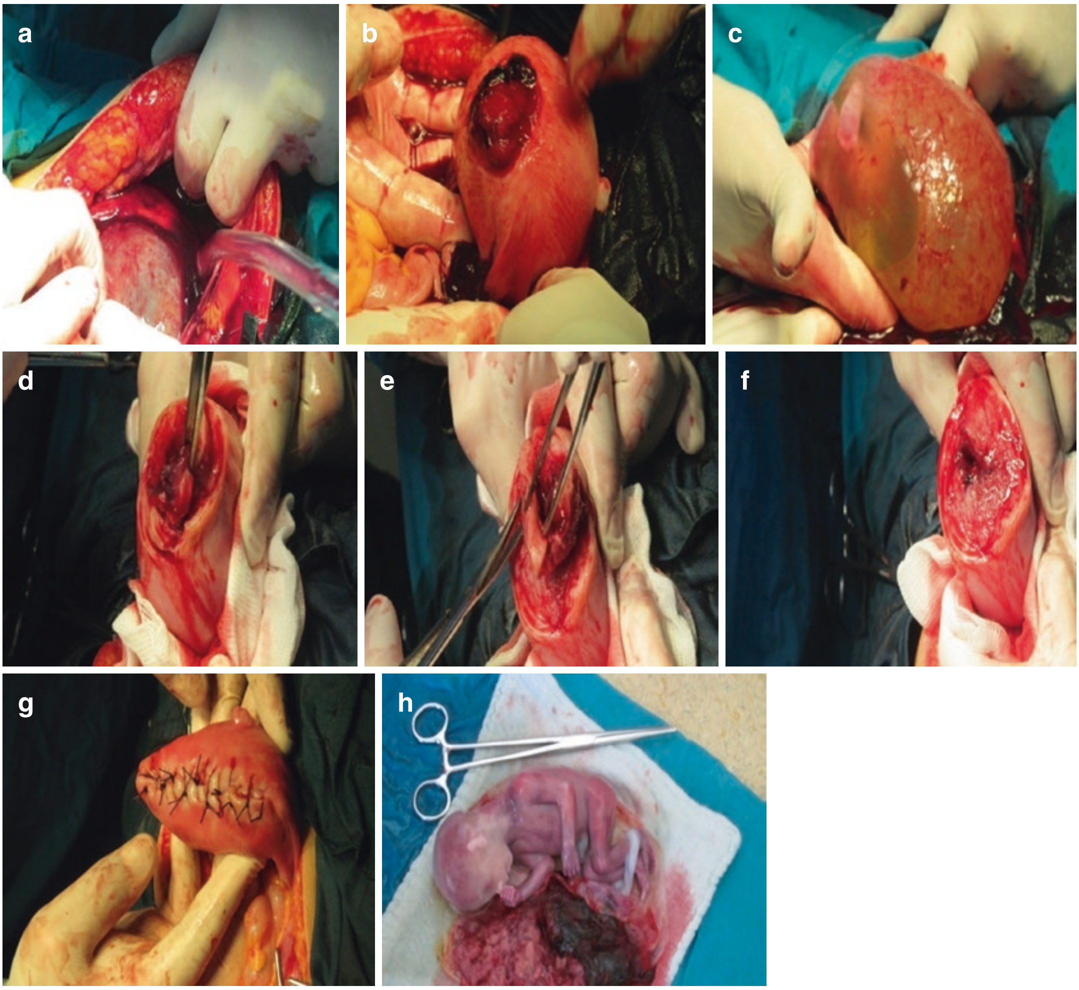


Fig. 15.22 (**a**) The gestational sac is in direct contact with the anterior wall; (**b**) placental implantation site; (**c**) the gestational sac; (**d**) fundal uterine wedge resection; (**e**) elimination of the placental villi; (**f**) the excised fundal myometrium before applying sutures; (**g**) mattress sutures of the excised fundal myometrium; (**h**) the excised placenta and the fetus. Reproduced from [174] under the CC Attribution License

If the organ to which the placenta is attached is removable, such as a section of bowel, then the placenta should be removed together with that organ [172]. In cases where placental implantation has occurred in vascular areas such as the mesentery and vital organs, it has been recommended that the placenta should be left in situ because surgical excision can result in uncontrollable and life-threatening hemorrhage [173]. If discovery is not made until attempted CS, even then a safer alternative would be to defer delivery if possible, close the abdominal incision, and transfer the woman to an appropriate hospital. This could be done even after the delivery of the fetus or neonate with the placenta left in situ if there is no bleeding [158].

Intraoperative steps of abdominal wall and attachment to the uterus are presented on Fig. 15.22.

Postoperative Management

Patients should remain in the intensive care for 24–72 h postoperatively. Complications may continue to occur for several weeks. A retained placenta can persist in situ for a number of weeks and has remained detectable for as long as 5 years [159].

Methotrexate can be used in the postoperative period to expedite absorption of the placenta. However, its use is controversial. It might increase infectious complications because of rapid tissue necrosis, but some authors argue for complete regression of the placenta. Methotrexate as a folate antagonist causes an acute intracellular deficiency of these folate coenzymes, thus affecting synthesis of DNA especially in rapidly multiplying cells. Methotrexate acts on rapidly dividing cells, and it is likely to have limited effects on the mature placenta with its limited proliferative activity. With or without its utilization, the retained placenta will frequently undergo suppuration and require surgical removal [144, 161]. Risks of secondary hemorrhage could be diminished while keeping the infection risk low. A case of placental infusion with methotrexate via the umbilical arteries has also been described [175]. Its use preoperatively, or alternatively the use of actinomycin D, has been proposed to destroy trophoblastic activity in cases with an established fetal death [176].

15.3.7.3 Anesthetic and Perioperative Management

See Chap. 21.

15.3.7.4 Prevention and Treatment of Preterm Labor

See Chap. 23.

15.3.8 Prognosis

15.3.8.1 Maternal Outcome

Abdominal pregnancy poses a serious threat to the survival of equally the mother and the fetus. Hence, it is vital that the diagnosis is made early in the pregnancy. Maternal mortality ranges 6–30% [127, 133, 159]. From 1809 to the 1970s, it was 18.2% [177]. This is principally due to the risk of massive hemorrhage from incomplete or entire placental separation anytime during pregnancy (see Sect. 15.3.7.2).

15.3.8.2 Fetal Outcome

Mortality

The fetal outcome tends to be poorer than the maternal outcome with perinatal mortality in range 40–95% [160, 178]. By a survey of the literature from 1809 to 1919, and questionnaires to 200 obstetricians, Beck was able to collect only 262 cases of extrauterine pregnancy after the fifth month with a living infant. Fetal abnormalities (congenital malformations) range 20–40%, mostly because of associated oligohydramnios [178]. However, with advanced pregnancy and if the fetus is surrounded by a normal volume of amniotic fluid, the fetal outcome tends to be better [159].

Morbidity/Deformations

Fetal deformation has been reported in the range 20–90%. Early amnion rupture can explain both the band-related defects, the compression-related defects, or a combination of the two [179].

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16 Spontaneous Uterine Rupture

Abstract

Nontraumatic uterine rupture is a rare but often catastrophic obstetric complication with an overall incidence of approximately 1/1536 pregnancies. In Western countries, it is five times less common. The vast majority of spontaneous uterine ruptures occur in women who have uterine scars, mostly as a consequence of previous Cesarean deliveries. The most consistent early indicator of uterine rupture is the onset of a prolonged, persistent, and profound fetal bradycardia. Other signs and symptoms, such as abdominal pain, abnormal progress in labor, and vaginal bleeding, are less consistent and less valuable in establishing the appropriate diagnosis. Labor-and-delivery suites should be able to start Cesarean delivery within 20–30 min of a diagnosis of fetal distress. In the case of fetal or placental extrusion through the uterine wall, irreversible fetal damage can be expected at that time; therefore, such a recommendation is of limited value in preventing major fetal and neonatal complications. However, action within this time may aid in preventing maternal exsanguination and death, as long as proper supportive and resuscitation methods are available before definitive surgical intervention can be successfully initiated.

16.1 Historical Perspective

One of the first descriptions of spontaneous uterine rupture (UR) was by Wilhelm Fabry (also William Fabry, Guilelmus Fabricius Hildanus, or Fabricius von Hilden) in the seventeenth century (Fig. 16.1). The first case was a multigravida during a labor at term with the UR due to fetal transverse lie. The second was a fatal case of UR caused by obstructed labor [1]. In James Dowling Trask's (1821–1883, one of the founders of the *American Gynecologic Society*) monograph on rupture of the uterus, 303 cases were recorded from 1700 to 1848; of these, only 38 were classified as ruptures during pregnancy, the others being cases of rupture during labor. On a careful examination of the notes in each of these 38 cases, it appears that the number must be considerably reduced—first, elimination of cases where the evidence that they were really cases of rupture of the uterus and not some other condition, for instance, abdominal extrauterine pregnancy, and, second, by removing those cases which were really cases of premature labor, the pregnancy having advanced nearly to term. When this reduction has been made, there remain 14 cases [2]. Cooper in 1858 described the postmortem findings of rupture of the uterus, in the third month of pregnancy, from tuberculous degeneration of the

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_16

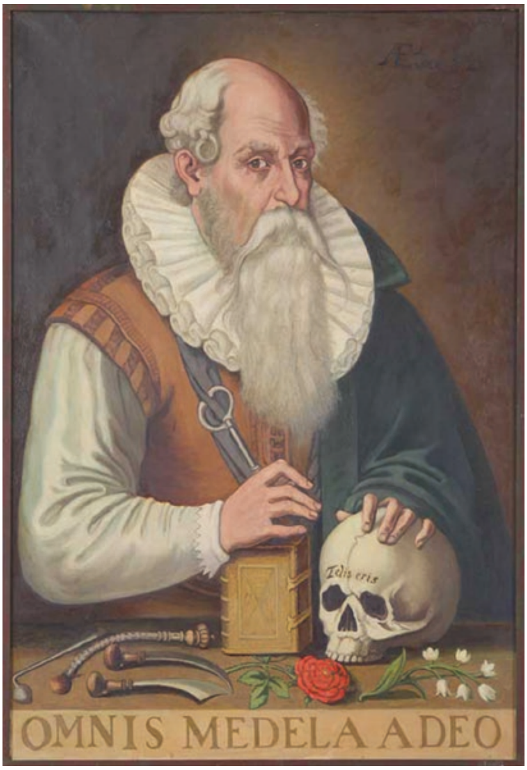

Fig. 16.1 Wilhelm Fabry (June 25, 1560–February 15, 1634), often called the "Father of German surgery," was the first educated and scientific German surgeon. He is the author of 20 medical books. His *Observationum et Curationum Chirurgicarum Centuriae*, published posthumously in 1641, is the best collection of case records of the century. Reproduced from [6] under the CC BY Attribution License

fundus [3]. Lustgarten quoted one case in the *British and Foreign Medico-Chirurgical Review*, one in the *Glasgow Medical Journal* in 1861, and further 17 cases collected by Lewers in 1887 [4]. In 1903, Baisch was able to record 37 instances of nontraumatic UR which occurred in the first 6 months of pregnancy [5].

16.2 Classification and Mechanisms

16.2.1 Definition

UR is defined as a disruption of the uterine muscle and visceral peritoneum or a uterine muscle separation with extension to the bladder or broad ligament. Rupture can be incomplete or complete.

Incomplete (partial) uterine rupture is present when the uterine wall is extremely thinned and the uterine muscular layer is lost but the uterine serosa (parietal peritoneum) is preserved (Fig. 16.2). One example is the laceration which opens from the uterus into the broad ligament but with the anterior and posterior leaves of this structure remaining untorn. Incomplete UR is mostly seen with scar dehiscence. In contrast to a frank UR, *uterine scar dehiscence* involves the disruption and separation of a preexisting uterine

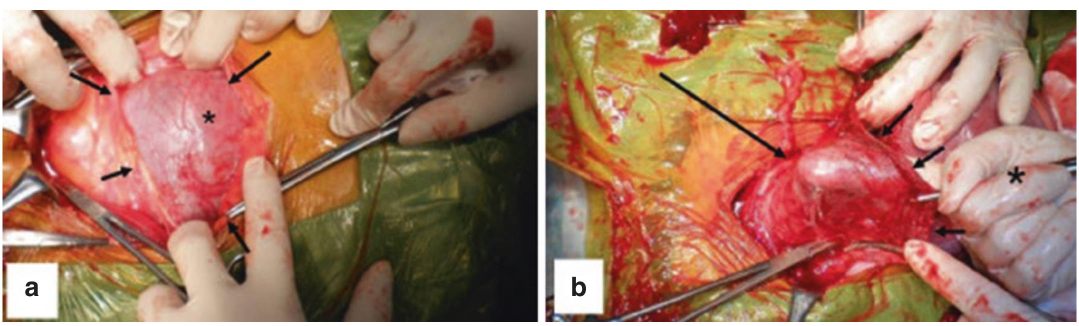

Fig. 16.2 Operative findings during a Cesarean section. (**a**) The asterisk indicates the thin anterior uterine wall, seen with a bulge caused by fetal parts from the inside. Arrows indicate the peritoneum. The left side of the photograph is the caudal side of the patient. (**b**) After delivering the fetus and removing the placenta, the thin wall was gently pushed from inside the uterus with a finger. The fingertip (*large arrow*) is clearly visible through the thin wall. The asterisk indicates the surgeon's right hand. Small arrows indicate the uterine incision site. Reproduced from [8] under the CC BY 2.0

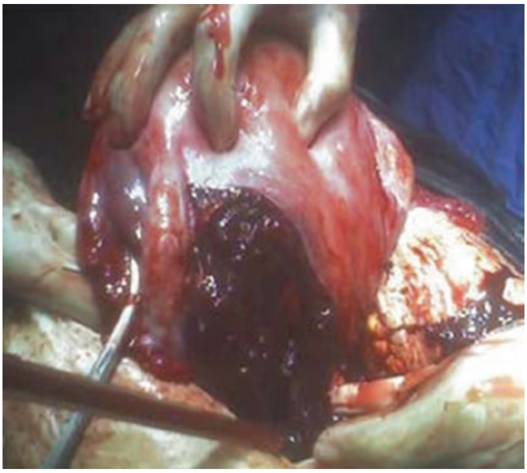

Fig. 16.3 Complete uterine rupture with a large left broad ligament hematoma with multiple small bleeding points from the branches of the uterine artery. Reproduced from [9] under the CC BY 3.0

scar after CS. Uterine scar dehiscence is a more common event than UR. Importantly, when the defect in the uterine wall is limited to a scar dehiscence, it does not disrupt the overlying visceral peritoneum, and it does not result in clinically significant bleeding from the edges of the preexisting uterine scar. In addition, in cases of uterine dehiscence (as opposed to UR), the fetus, placenta, and umbilical cord remain contained within the uterine cavity.

Complete uterine rupture is present when rupture occurs through all layers of the uterine wall including serosa with or without accompanying bleeding or hematoma (Fig. 16.3). Therefore, the amniotic cavity directly communicates with the abdominal cavity. Approximately 70% have a complete rupture and 25% an incomplete rupture. Seventy percent of scar ruptures presented with complete rupture [7].

16.2.2 Classification

There are several classification systems for UR according to the etiology. It may be classified into three groups: (1) those involving dehiscence of a CS scar, (2) those secondary to trauma to an intact uterus (see Chap. 10), and (3) those involving spontaneous rupture of an intact uterus [10]. *True* spontaneous rupture of the pregnant uterus is defined as a partial of full-thickness separation of the uterine wall before the onset of myometrial contractions that occurs primarily in the third trimester when the intrauterine volume and pressure are increased to the highest possible levels. Unfortunately, many cases were published under the term spontaneous but are not really true spontaneous URs.

Schrinsky and Benson in 1978 [11] made etiology-based classification which was further updated and expanded (Table 16.1).

Table 16.1 Classification of causes of uterine rupture during pregnancy [11–13]

1. Traumatic rupture
(a) *Instrumental*
• Uterine sound or curette
• Manual removal of placenta
• Various tools for legal or criminal abortion
(b) *Violence: direct or indirect*
(c) *Obstetric*
• Oxytocins, forceps, and breech extraction
• Intrauterine manipulation: internal version, forceps rotation, and shoulder dystocia
• Fundal pressure
• Hydrocephalus
• Neglect: cephalopelvic disproportion and transverse lie
2. Spontaneous rupture
(a) *Previous uterine surgery*
• Cesarean section (scarred uterus)
• Myomectomy
• Salpingectomy
• Ventrofixation
• Curettage or manual removal of the placenta
(b) *No previous surgery*
• Congenital uterine abnormality
• Cornual pregnancy
• Hydatidiform mole or chorioadenoma destruens
• Placenta percreta
• Genetic susceptibility for rupture (Loeys–Dietz syndrome)
• Red degeneration of fibroid
• Chronic corticosteroid use
• IVF?
• No apparent cause
3. Combinations

Rickards in 1938 described five types of rupture of the scarred uterus during pregnancy [14]:

Type I: the rupture occurs through an old upper-segment incision, and the placenta is situated away from the uterine scar. Characteristics include:

- The rupture tends to take place during labor
- Little or no hemorrhage with a normal pulse
- The pain may become niggling in type after the scar has started to give way
- The bulging bag of membranes may sometimes be palpated through the abdominal wall
- Prognosis is good provided that suitable treatment is available

Type II: The rupture occurs through an upper-segment incision, and the placenta is situated underneath the old scar. This type is more serious. When the placenta is situated underneath the old scar, a gradual erosion of fibrous tissue by the placental villi occurs [15]. This erosion is an insidious one and may cause marked attenuation of the scar during the latter part of pregnancy. The rupture is more liable to occur before the onset of labor. The eating away of the scar may be associated with vague pains in the lower abdomen [16]. As the process is gradual, hemorrhage is seldom severe. Characteristics include:

- Gradual rupture tends to occur toward the end of pregnancy. This may be accompanied by vague pain in the lower abdomen.
- After the onset of labor, hemorrhage occurs and may be of considerable severity.
- Prognosis will not be so favorable as in type I and will depend very largely on the amount of intra-abdominal hemorrhage.

Type III: The rupture occurs after a previous lower-segment CS. Characteristics include:

- Rupture takes place during labor.
- Hemorrhage may occur, due to the extension of the laceration laterally into the uterine arteries.
- The bladder may be involved (rarely), giving rise to hematuria.

Type IV: The rupture is complete, through an upper-segment incision, and the child, within its bag of membranes, is expelled into the abdominal cavity, the placenta remaining in situ. The uterine scar gives way along its entire length, the contractions persist, and the child is extruded into the abdominal cavity. The fetal heart sounds almost invariably disappear and fetal movements cease. The uterus is felt to be pushed over to one side, and the child, floating in the abdominal cavity, is very easily palpable. Characteristics include:

- Fetal heart sounds cease as a rule
- Fetal movements usually stop
- The uterus is pushed over to one side
- The fetus, lying free in the abdominal cavity, is easily palpable

Type V: The rupture is complete, through an upper-segment incision, and the child, with its placenta, is extruded completely into the abdominal cavity. Characteristics include:

- Often associated with severe intra-abdominal hemorrhage
- Fetal heart sounds are absent
- Fetal movements are absent
- The uterus is pushed over to one side
- The fetus, lying free in the abdominal cavity, is easily palpable

16.2.3 Mechanisms of Uterine Rupture

16.2.3.1 Scarred Uterus

Uterine Scar Rupture

Patients with uterine scar are more likely to have uterine scar rupture as a result of attempted trial of labor and the poor monitoring of labor [17]. In scarred uteri, the vast majority of uterine dehiscence and ruptures will occur via the uterine scar. The atrophic, inelastic nature of the scar renders it less adaptive to forces in labor, predisposing to rupture. Prostaglandins induce local biochemical modifications that weaken the scar, predisposing

it to rupture [18]. In trial labor, secondary inertia may indicate that the mechanism of labor has been interfered with by a partial or complete rupture. It is postulated that blocking of the neuromuscular impulses is caused by the break in the continuity of the muscle [19].

Atypical Site Rupture

A particularly rigid anterior lower segment may cause the abnormal distribution of force. During retraction, the posterior wall may be excessively shortened and thinned due to the rigid anterior uterine scar, catalyzing atypical UR via healthy tissue. Any factor compromising uterine structural integrity or causing the abnormal distribution of force can precipitate UR. The site of UR is unpredictable and may be atypical.

The lower-segment UR is the most common (60%) site of rupture [20–23] with the anterior transverse location being the most common [24]. The second most common location is an extension to the broad ligament, and other locations have an incidence of around 5% [24]. Mostly there are no differentiations between rupture caused by obstructed labor and scarred uterus. Rupture is complete in around 73% cases and incomplete in 27% [20, 21, 23].

Posterior (posterolateral) UR complicating vaginal birth after low-transverse CS is rare [25–29]. Fetal malposition with an occipitoposterior position contributes to posterior UR (Fig. 16.4), as does malpresentation with a transverse lie [28, 29]. Malposition alters the distribution of contractile force and increases labor dystocia; certain malpresentations cause uterine hyperdistention, which may also precipitate atypical UR. Prostaglandins generating excessive uterine activity have been assumed to be the cause of UR. Prostaglandins may cause excessive uterine activity that results in a posterior wall sacculation in the face of a strong anterior scar [27]. During the second stage of labor, with the fetus undergoing cardinal movements, UR occurs through the weakened posterior wall. In 50% the labor was induced by prostaglandins, suggesting other factors may play a role [29]. The presence of an inelastic scar comprised of fibrous tissue on the anterior wall prevents even distribution of forces of contraction. As uterine muscle undergoes retraction during the active phase of labor, the healthy posterior wall may undergo excessive shortening and thinning compared to an inelastic anterior wall, which could predispose to rupture.

Fig. 16.4 Vertical posterior rupture of scarred uterus due to occipitoposterior position of the fetus. Reproduced with permission from [28]

16.2.3.2 Unscarred Uterus

Obstruction as a cause of UR and the delay in accessing qualified care is found in developing counties with patients without antenatal care. The causes of UR during labor may briefly be described as follows: some obstruction exists opposing the advance of the child, whether the obstruction is pelvic contraction, unusual size of the child, or malpresentations. The uterus continues to contract, and thickening of the upper part of the uterus occurs, while its lower segment becomes thinned. If assistance is not given, the lower segment becomes more and more thinned and finally ruptures.

> The rupture of the unscarred uterus during labor almost always begins in the lower segment.

A uterus emptied of its contents by their extrusion into the peritoneal cavity may retract firmly, thus preventing hemorrhage from the placental site and from the wound in the uterus. The fetus and placenta do not necessarily escape at once or at all. It is the most common cause of spontaneous rupture during pregnancy and labor ranging from 68.5 to 73.2% [17, 30] in developing countries. In developed countries, it is significantly lower starting from 13% [31].

16.3 Incidence

16.3.1 Developed/Undeveloped Country

In spite of the recent advances in modern obstetric practice, it remains a life-threatening complication of pregnancy and labor especially in the developing world [32]. Table 16.2 shows the differences in incidence between countries.

There are several issues while trying to obtain the true incidence. First, especially in Africa, registration of births occurring at home is incomplete, although the number of patients who deliver at home and only seek medical attention when problems occur is decreasing. Second, a number of maternal deaths occur in the rural areas before hospital admission without known and registered cause of death. There are also significant differences between regions in the same country. The incidence of 1/167–1/200 deliveries was found in Southwest Nigeria [37, 38, 65], while in the Northwest Nigeria, it was more than double (1/77 deliveries) [41, 42]. Third, because of the health reform policy of the government in many countries, which prohibits refusal of admission of any medical emergency in all the state-owned public hospitals, larger hospitals receive many of the complications of labor that occur in the primary and secondary health facilities and the various private hospitals. Therefore, the real incidence distribution among hospitals is not known. Fourth, some studies report cumulatively spontaneous (scarred and unscarred uterus) and sometimes traumatic URs [38]. Reports from Nigeria, Ghana, Ethiopia, and Bangladesh indicated that about 75% of cases of UR were associated with

Table 16.2 (Spontaneous) uterine rupture rates across the world (in decreasing incidence)

Country	Incidence
Ethiopia [30, 33]	1/38–1/175
Uganda [17, 34]	1/93–1/200
Pakistan [35]	1/100
Yemen [36]	1/159
Nigeria	
Southwest [24, 37–39]	1/186–1/416
Rural [40]	1/112
Northwest [41, 42]	1/77
Guinea [43]	1/199
Morocco [44]	1/222
Sudan [45]	1/246
India [46, 47]	1/357–1/714
Kenya [48]	1/425
Libya [49]	1/585
Iraq (Basra) [50]	1/801
Turkey [51]	1/966
Saudi Arabia [52]	1/1011
Nepal [7]	1/1100
Australia [53]	1/1163
Zimbabwe [54]	1/1285
Rep. of South Africa [55]	1/1362
Trinidad [56]	1/1500
Bahrain [57]	1/2213
Tunis [13]	1/2581
Kuwait [58, 59]	1/1851–1/3333
Canada [60]	1/3333
Taiwan [61]	1/3871
Ireland [62]	1/4348
Qatar [63]	1/4968–1/6843
Singapore [64]	1/6331
United States [10]	1/8000–1/15,000

the unscarred uterus [66]. Recent reports suggest that the incidence, particularly of a spontaneous rupture, may be on the increase in industrialized countries (see Sect. 16.3.1).

For developed countries, the data available indicate that the prevalence of UR for women with previous CS is in the region of 1%, whereas for women without previous CS, it is extremely rare (<1/10,000). Overall, the rates are below 1/1000 [67].

16.3.2 Decade Dependency

The incidence is decade dependent. The incidence of UR in the United States between 1967 and 1978 was 1/1000–1/1500 deliveries, but

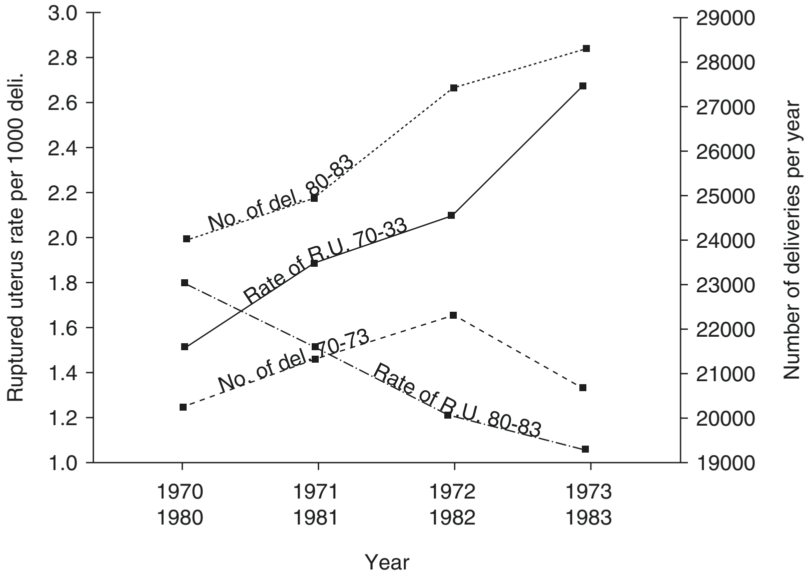

Fig. 16.5 Comparison between the total number of deliveries in 1970–1973 and 1980–1983 in relation to the rate of ruptured uterus per 1000 deliveries in those years (The numbers for 1983 are a multiplication of the first 6 months) (*R.U.* rupture of the uterus). Reproduced with permission from [69]

spontaneous UR accounted for 25% of the total, and only 17% of these occurred before the onset of labor [11]. After two decades, the incidence of spontaneous rupture of the unscarred uterus ranged from 1/8000 to 1/15,000 deliveries [10, 68]. Due to the rarity of the spontaneous UR, most studies have a study interval of around a decade to collect enough number of patients sufficient for the analysis and comparison. With the progress of medicine and knowledge of the risk factors, the incidence is decreasing, but there are still significant differences between developed and undeveloped/developing countries (Fig. 16.5).

16.4 Risk Factors

Most cases of spontaneous UR in undeveloped/developing countries are due to rupture of the unscarred uterus secondary to neglected obstructed labor, while CS scar or scarred uterus rupture is the most common cause in developed countries [65]. In developed countries, rupture of the unscarred uterus is severalfold lower than that of scarred uterus involving 1/17,000–1/20,000 deliveries [20].

Reports of the presentation and the management of UR in the first or second trimester are limited [70–75]. Usually, it is either associated with cases of trophoblastic tumor or pathological invasion of the placenta through the uterine wall, for example, placenta increta or percreta [76]. Uterine malformation(s) associated with pregnancy, such as a rudimentary horn, may cause spontaneous UR or rupture after surgical/obstetric intervention during pregnancy [77]. It may also happen in cases of uterus scarred due to the previous myomectomy, in previous CS scars, or previous operative laparoscopy [73, 78]. Exceptionally, there are cases of spontaneous UR associated with red degeneration of a fibroid in a gravid uterus [12].

16.4.1 Scarred Uterus

Previous CS is the most important predisposing factor for the occurrence of UR [32], and so-called *scarred uterus* (uterine scars from any type of CS) is present in up to 65% of cases [52, 79]. It is conventionally attributed to the structural compromise of the uterine scar, as depicted by the term “trial of scar.” The rate of CS has risen from 5% in 1970 to 26% in 2002 despite improvement in nonoperative obstetric procedures [80]. Relevant to this issue of vaginal birth after CS (VBAC) is that the overall rate in the United States increased from 3.4% in

1980 to a peak of 28% in 1996. Commensurate with this eightfold increase in the VBAC rate, reports of maternal and perinatal morbidity also increased, in particular with reference to UR. By 2007, the VBAC rate in the United States had fallen to 8.5%. Not surprisingly, the CS rate also reached an all-time high of 32% in 2007. In its recent guidelines pertaining to VBAC, the *American Congress of Obstetricians and Gynecologists* (ACOG) adopted the recommendation not to restrict women's access to VBAC [81]. This occurred after the *National Institutes of Health Consensus Development Conference Panel* reviewed the totality of the evidence concerning maternal and neonatal outcomes relating to VBAC [82]. Rupture of the pregnant uterus affects 0.7–1.9% of women with previous CS attempting a trial of labor [83]. The reported recurrence rate for UR is 4.8–19% with the highest rates seen in women with a history of a ruptured upper uterine segment (classic scar). In these cases planned CS is recommended [84].

16.4.1.1 Classic Cesarean Delivery

Classic CS via vertical midline uterine incision is currently infrequently performed and account for 0.5% of all births in the United States [85]. There is 11.5% absolute risk of UR in women with classic vertical CS scars who underwent an unplanned trial of labor after CS (TOLAC) [86]. For women who underwent repeat CS, the UR rate for women with prior classical uterine CS scars was 0.64%. All patients underwent repeat CS, but a high rate of preterm labor resulted in 49% of the patients being in labor at the time of their CS [85]. An absolute UR rate in women with a previous classic, inverted *T*, or *J* incision that either presented in advanced labor or refused repeat CS was 1.9% [87]. These rates of frank UR in women with classic CS are in contrast to the higher rates of 4–9% that the ACOG had historically reported for women with these types of uterine scars [88]. However, there is a 9% rate of asymptomatic uterine scar dehiscence [85]. This result suggests that disruptions of uterine scars might have been misclassified as true ruptures instead of dehiscences in previous studies; this error may explain the bulk of the discrepancy.

16.4.1.2 Low-Vertical Cesarean Section

There is a 1.1% absolute risk of symptomatic UR in women undergoing a TOLAC with a low-vertical CS scar [87, 89]. Compared to women with low-transverse CS, there is no significantly increased risk of UR or adverse maternal and perinatal outcomes. Interpretation is hampered by inconsistencies in how high the lower uterine segment could be cut before it was considered a classic incision. Even when the lower uterine segment is already well developed as a result of active labor, a low-vertical incision of adequate length is often impossible to permit fetal delivery. *The classic extension* is arbitrarily defined as a 2 cm extension into the upper segment, and the overall rate of UR was 0.62%. This rate could be further divided as 1.15% for women who underwent a TOLAC compared with no ruptures among women who underwent elective repeat CS [89].

16.4.1.3 Unknown Uterine Scar

In many instances, the type of incision used for a prior CS cannot be confirmed due to unavailability of the operative report. Under these circumstances, the assessment of UR risk may sometimes be guided by the obstetric history to infer the most probable type of uterine scar. For example, a patient with a history of a preterm CS at 28 weeks of gestation has a much higher likelihood of having had a vertical uterine incision than a patient who underwent a CS for an indication of the arrest of fetal descent at term. It has been argued that because most CS in the United States are accomplished via low-transverse uterine incisions, the risk of UR for patients with an unknown scar is similar to that for women who have previously undergone a low-transverse hysterotomy. This logic depends on the high ratio of low-transverse to vertical incisions performed for CS, but it ignores the varying probability with which different types of uterine incisions are made under different obstetric circumstances, as well as differences that occur due to varying medical resources and the prevailing local practitioner practices in countries other than the United States. An estimated 20,000 African refugees enter the United States each year, 80% from countries were upper uterine segment CS is

not an uncommon practice. Immigration of African refugees to Europe is becoming increasingly common. Nevertheless, the vast majority of CS performed in the United States are accomplished via low-transverse uterine incisions.

Small case–control studies, despite being underpowered, did not find an association between an unknown uterine scar and the risk of UR [90, 91]. The *Maternal-Fetal Medicine Units Network Cesarean Delivery Registry* reports a 0.5% risk of UR for patients who underwent a TOLAC with an unknown uterine scar [87]. A small, randomized, controlled trial compared labor augmentation with oxytocin with no intervention in women with prior CS involving either one or two unknown uterine incisions. All uterine dehiscences and ruptures occurred in the group that underwent labor augmentation [92].

16.4.1.4 Low-Transverse Cesarean Section

The myometrium from scarred low uterine segment has a higher collagen content compared with unscarred myometrium from laboring women, but not unscarred myometrium from nonlaboring women [93]. The risk of UR after a low-transverse CS varies depending on whether patients undergo a TOLAC or an elective repeat CS and on whether labor is induced or spontaneous, as well as other factors. Today, the vast majority of CS is of the low-transverse type. For women who have had one previous CS, examining the various risk factors for UR is instructive. It should be noted that CS has its potential complications including an increased risk of placenta previa and accreta with every subsequent repeat CS, resulting in higher rates of peripartum hysterectomy [94]. The trend of increasing rate of UR with increasing maternal age was noted [95, 96]. Age-related decrease in myometrial strength [97] and defective wound healing [98] could be the contributing factors.

16.4.1.5 Cesarean Section Without a Subsequent Trial of Labor

The spontaneous UR rate among women with a single CS scar who underwent scheduled repeat CS without a TOLAC is 0.16% [99]. This finding indicates that uteri with CS scars have an intrinsic propensity for the rupture that exceeds that of the unscarred organ during pregnancy, which is 0.012% (OR 12). Therefore, all other UR rates in women with a previous CS should be referenced to this expected baseline rate.

16.4.1.6 Cesarean Section with Subsequent Spontaneous Labor

The UR rate among women with a single previous CS who labored spontaneously during a subsequent singleton pregnancy is in the range of 0.45–0.72% [99, 100]. This rate of UR implies an increased relative risk of 3–4 for women who labor spontaneously compared with women who undergo elective repeat CS.

16.4.1.7 Cesarean Section with Subsequent Augmentation of Labor

Despite the clinical heterogeneity and different VBAC success rates for women undergoing spontaneous labor rather than either labor augmentation or induction, the data that do exist are conflicting. There is a wide variance in the frequency of clinical use of oxytocin as well as in the dose and dosing schedules of oxytocin. As a result, there is a paucity of specific evidence-based clinical guidelines for the use of oxytocin in VBAC trials. The rate of UR in women who underwent oxytocin augmentation of labor after a previous CS was 0.9–1.4%, compared with 0.34–0.4% in women who underwent a trial of spontaneous labor (twofold to fourfold increased risk) [82, 101]. Others claim that labor augmentation with oxytocin (and duration of oxytocin administration) did not significantly increase the risk for UR in the scarred or unscarred uterus [100, 102]. However, the conclusions to be drawn from this are both limited and suspect because, in general, no proper adjustments have been made. Therefore, the duration of labor and not oxytocin use itself may predispose the patient with or without a uterine scar to rupture. The problem in some studies from developing countries is a high percentage of its use; 41.7% of the respondents were given this drug (all but one had it through intravenous infusion) [36]. Oxytocin was used for augmentation of already prolonged and obstructed labor rather

than for active management of labor concluding that the supervision and control over this drug are missing. In this regard, assessment of the safety of oxytocin use in VBAC trials must consider both the dosage and the time of exposure. At an intravenous oxytocin dosage range of 6–20 mU/min, a more than threefold increased risk of UR was associated with oxytocin use. At a dosage range of more than 20 mU/min, a nearly fourfold increased risk of UR was noted. The attributable risk of UR associated with oxytocin use was 2.9–3.6% for the maximum oxytocin dose ranges of more than 20 mU/min and more than 30 mU/min, respectively. There was no significant risk association between time (in terms of both duration of oxytocin exposure and duration of labor) and UR risk [103].

> The upper limit of 20 mU/min of oxytocin for use in VBAC trials is recommended with monitoring of oxytocin for both labor augmentation and induction.

Newer studies claim that when oxytocin exposure is considered, induction of labor and augmentation of labor have similar risks of UR, although both induction and augmentation of labor are associated with increased risk of UR compared to women who labor spontaneously. The initial cervical exam impacts this finding; an unfavorable initial cervical exam (<4 cm dilation) results in an increased risk of UR compared to spontaneous labor [104].

The benefit of intrauterine pressure catheter (IUPC) monitoring of uterine contractions in VBAC trials is unclear, with only a single small case series failing to detect differences in fetal or maternal morbidity/mortality associated with UR when an IUPC was used instead of external tocodynamometry.

> The intrauterine pressure catheter is useful in allowing careful titration of oxytocin dosing, especially when maternal habitus poses a limit to the accurate external monitoring of uterine contractions in women undergoing a TOLAC.

16.4.1.8 Cesarean Section and Induction of Labor

Induction of labor is an increasingly common practice in the United States and accounts for at least 20% of all births. While oxytocin is an effective drug in patients with favorable Bishop scores, other pharmacological or mechanical agents are frequently utilized in the event of an unripe cervix. Induction of labor after a prior CS appears to be associated with an increased risk of UR. The rate of UR that underwent labor induction after a single previous CS was 1.4–4% compared with 0.34–0.72% for women who had labored spontaneously [100, 101]. These findings suggest fourfold to even 12-fold increased risk of UR for women who undergo labor induction after previous CS, dependent on the labor induction method.

Prostaglandins

> ACOG guidelines discourage the use of prostaglandins to induce labor in most women with a previous CS. This is based on evidence for an increased risk of uterine rupture associated with misoprostol [81].

Several studies found a severalfold (3–5% compared to <1%) increased risk for UR when prostaglandins were used in gravidas who underwent a TOLAC [99, 100]. In contrast, two studies did not show the significant difference, but in both studies, patients with induction of labor had a higher percentage of spontaneous uterine perforations [105, 106]. Landon et al. reported no URs [87]. Although the study was underpowered to detect small differences, the particular type of prostaglandin administered did not appear to significantly affect the UR rate (misoprostol, dinoprostone, PGE_2 gel, and combined prostaglandins) [87]. When reviewing all studies on misoprostol induction in patients with a previous CS, calculated risk of UR of 4.7% was compared to an overall rupture rate of around 1% associated with a vaginal birth without misoprostol after a previous CS (fourfold increase) [107, 108].

In women with previous CS, myometrial contractions are associated with a decrease in total myometrial collagen and possibly connective tissue content, and that incubation with misoprostol accentuates such effect, while exposure to dinoprostone does not. The more pronounced contractile response and a decrease in collagen content observed with misoprostol may explain the higher incidence of UR observed with its use in women with previous CS, who usually experience UR at the site of their old scar when treated with PGs for cervical ripening as compared to other agents [18]. The milder effects of dinoprostone on collagen content seem to suggest that it may represent a safer choice for labor induction in the setting of a previous CD [109].

Mechanical Methods

Data on mechanical methods of labor induction for cervical ripening are limited but reassuring. In a small case series, there was no statistically significant difference among the UR rates of 1.1% for spontaneous labor, 1.2% for induction by amniotomy with or without oxytocin, and 1.6% for induction by transcervical Foley catheter [110]. Conversely, Hoffman et al. reported a 3.67-fold increased risk of UR with Foley catheter use for preinduction cervical ripening. Importantly, however, many of these patients received concomitant oxytocin [111]. A randomized controlled trial found that the addition of oxytocin to the use of a transcervical Foley catheter for labor induction does not shorten the time to delivery and has no effect on either the likelihood of delivery within 24 h or the vaginal delivery rate [112].

> Induction of labor with a transcervical Foley catheter alone may be a reasonable option for women undergoing a TOLAC with an unfavorable cervix.

16.4.1.9 Cesarean Section with Previous Successful Vaginal Delivery

There is a protective association of previous vaginal birth on UR risk in subsequent attempts at vaginal birth after previous CS with around one-fourth to one-fifth of the risk [113]. In women with no prior vaginal delivery who underwent a TOLAC, there is an increased risk of UR with induction versus spontaneous labor (1.5% vs. 0.8%). In contrast, no statistically significant difference was shown for women with a prior vaginal delivery who underwent spontaneous TOLAC compared with labor induction (0.6% vs. 0.4%) [114].

16.4.1.10 Cesarean Section with Subsequent Successful VBACs

Studies suggest a protective advantage with regard to the UR rate if a woman has had a prior successful VBAC attempt. Multiple potential explanations exist, but the two most obvious are that a successful prior VBAC attempt assures that (1) the maternal pelvis is tested and that the bony pelvis is adequate to permit passage of the fetus and (2) the integrity of the uterine scar has been tested previously under the stress/strain conditions during labor and delivery that were adequate to result in vaginal delivery without prior UR. The rate of UR decreases after the first successful VBAC, but that there are no additional protective effect demonstrated thereafter: the UR rate was 0.87% with no prior VBACs, 0.45% for those with one successful prior VBAC, and 0.43% for those with two or more successful prior VBACs [115]. Pooled data indicate an increased UR rate of 1.4% in failed VBAC attempts that required a repeat CS in labor [87, 101].

16.4.1.11 Interdelivery Interval

When an interpregnancy interval between CS and a subsequent pregnancy of <18 months, UR was nearly three to four times as common in comparison with control [116, 117]. A Canadian study on women who underwent a TOLAC after a single low-transverse CS found that 2.8% of patients who had an interdelivery interval of ≤24 months had a UR compared with 0.9% for those with an interdelivery interval of >24 months (OR 2.65) [118]. In a follow-up study, the same authors examined the risk of UR between 18 and 24 months. After adjustment for confounding factors, an interdelivery interval shorter than 18 months was associated with a significant increase of UR (OR 3), whereas an

interdelivery interval of 18–24 months was not (OR 1.1) [119].

> An interdelivery interval shorter than 18 months but not between 18 and 24 months should be considered as a risk factor for uterine rupture after previous CS.

The authors speculated that a prolonged interpregnancy interval may allow time for the previous CS scar to reach its maximal tensile strength before the scar undergoes the mechanical stress and strain with a subsequent intrauterine pregnancy. Interestingly, the authors also observed that the combination of a short interdelivery interval of ≤24 months and a single-layer hysterotomy closure (see Sect. 16.4.1.12) was associated with a UR rate of 5.6%, a rate approximately three times higher than patients without this combination. This is comparable to the rate of UR for patients undergoing a TOLAC with a previous classic midline CS scar [118]. There were no comparisons of single- or two-layer suture in these studies.

16.4.1.12 Single-Layer Versus Two-Layer Hysterotomy Closure

Several techniques for myometrium closure have been described, including the use of interrupted, locked, and unlocked continuous sutures with single- or double-layer closure [120, 121]. Single-layer locked, continuous suturing, popularized in North America during the late 1980s, is part of the Misgav–Ladach technique developed by Stark et al. [121, 122]. A single-layer closure might have several short-term benefits, including reduced operating time, decreased blood loss, reduced tissue disruption, and the reduced introduction of foreign suture material into the wound. Most studies [123, 124] compared a locked single-layer closure with a double-layer closure; it is, therefore, possible that many benefits are related to tissue strangulation by locked sutures, which results in better and faster hemostasis. However, few conclusions can be drawn about the short-term benefits of locked versus unlocked single-layer closures because studies specifically comparing these two closure types are lacking [125]. One large randomized controlled trial did not confirm reduced operating time and blood loss of a single-layer closure [126].

Bujold et al. found a four- to fivefold increased risk of UR after previous single-layer uterine low-transverse closure (3.1%) compared to a two-layer closure (0.5%) for CS [127], and the recommendation was that single-layer closure should be avoided in women who contemplate future VBAC delivery [127, 128]. Locked but not unlocked single-layer closures were associated with a higher UR risk than two-layer closure in women attempting a TOLAC [123]. These findings are in agreement with a hypothesis that an unlocked single-layer closure leads to better uterine scar healing. Their view is based on the fact that locked sutures increase pressure at the suture–tissue interface, which can cause ischemic necrosis, impairing coaptation. Meanwhile, unlocked sutures provide coaptation, hemostasis, and wound strength in the immediate postoperative period [129]. Should the wound be exposed to additional pressure, an unlocked suture would provide more strength than a locked suture. Final conclusions cannot be drawn because information on the suture type (locked or unlocked) for the first or second layer of a double-layer closure was usually not available, and this parameter could have influenced the comparison between single- and double-layer closures. In addition, other factors such as suture material, the inclusion or exclusion of decidua in the uterine suture, and certain risk factors for UR, including fetal macrosomia, labor dystocia, and labor induction, were not taken into account. Decidua inclusion in sutures or eversion of the edges could result in a weaker scar and could explain the difference between single-layer locked, continuous closure and double-layer closure [95, 130, 131].

> Single-layer locked, continuous closure may increase the risk of uterine rupture in women attempting TOLAC in a future pregnancy. The risk of uterine rupture after an unlocked single-layer closure seems to be comparable with that after a double-layer closure.

Uterine closure with chromic catgut alone, irrespective of the number of layers, also resulted in a higher incidence of the abnormal lower uterine segment [95]. The rapid proteolytic degradation of chromic catgut, especially in the presence of infection, could be the reason [132].

16.4.1.13 Multiple Cesarean Sections

Multiple CS carry a higher risk for UR than a previous single CS. Studies from 1993 to 2010 showed that the risk of UR in a subsequent pregnancy ranged from 0.9 to 6.0% (1/17–1/108). This risk is increased 2–16 times compared to women with only a single previous CS [133–135]. Women with a previous vaginal delivery were about one-fourth as likely to have a UR as women without a previous vaginal delivery (OR 0.26) [113]. The 2004 ACOG recommendation was revised in an updated 2010 guideline to suggest that women with two previous low-transverse CS may be considered candidates for TOLAC regardless of their prior vaginal delivery status [81]. There is only one study with findings contrasting with all these reports where there was no statistically significant difference in UR between single and multiple previous CS [136].

16.4.1.14 Placenta Percreta

The suggested incidence of abnormal placentation, including placenta percreta, varies between 1/540 and 1/93000 with an average of 1/700. Recently, the incidence of placenta accreta is rising due to increased number of CS in modern obstetrics [137]. Spontaneous rupture of the uterus due to placenta percreta is one of the most urgent obstetrical complications resulting in rapid exsanguination and high mortality which is more commonly seen in the third trimester and is very rare in the second trimester [137]. It is rarely recognized intrapartum and is very difficult to diagnose. The precise etiology of all cases of placenta accreta is unknown; however, there are known factors that increase the risk. Greatest among them are scarring of endometrial cavity with previous CS, uterine curettage, myomectomy, Asherman's syndrome, iatrogenic uterine perforation, and advanced maternal age. These risk factors are frequently seen in IVF/embryo transfer. In most cases, placenta accreta is caused by a combination of factors, and its occurrence is it unlikely to be attributed to a single factor. In most reports, a placenta percreta was diagnosed in patients with the previously scarred uterus [138, 139]. It was described in an unscarred uterus but with previous uterine instrumentations (including IVF procedures) [140].

UR caused by placenta percreta mainly occurs during the later period of pregnancy, with very few reports of its occurrence during the first trimester [141, 142]. In most cases of URs that occur during delivery, the affected site is the lower uterine segment; however, in cases of UR during the first trimester, the site commonly affected is the fundus [141, 142].

16.4.1.15 Sexual Intercourse

There are several case reports describing UR of scarred uterus following sexual intercourse [143, 144]. The issue is whether it should be labelled spontaneous or included in the group of traumatic URs. Also, it is not known whether intercourse was accused as a possible cause in other reports of spontaneous UR without any etiology revealed.

16.4.2 Unscarred Uterus

Back in 1845 Jackson confirmed M'Keever's observations about risk factors for UR: "I can fully bear out the opinion of Dr. M'Keever, in his Essay [145], that this dreadful accident occurs more frequently amongst the lower ranks than the higher; and I would suggest whether this result does not arise from the greater frequency of deformity of the pelvis as the consequence of rachitis or scrofula in the former class; and hence, it is highly probable that in large towns, where poverty and unhealthy occupants prevail, and especially where children are engaged in cramped or restrained positions, as in cotton factories, we shall find a higher ratio of this kind of difficult and dangerous parturition" [146].

The anterior wall, particularly in the lower segment, is the commonest site of rupture of an unscarred uterus [37, 38, 71]. Spontaneous rupture usually involves the lower segment and occurs

during labor, as women with upper-segment scars are delivered by CS before the onset of labor [72].

16.4.2.1 Oxytocin and Prostaglandins

For the stimulation of inert labor, the following postulates for safe administration of oxytocin have been suggested:

1. Labor should be true, not false
2. The inertia should be of the hypotonic variety
3. Wait until the cervix is two fingerbreadths dilated
4. The oxytocin should be adequately diluted or divided and given over a safe period of time
5. There should be no disproportion and no scar in the uterus
6. Constant attendance of medical staff is mandatory for administration of a suitable anesthetic if the uterus should react violently
7. The fetal heart should be frequently auscultated
8. Hesitate to use oxytocin if the patient has had more than four babies
9. If there should be, any doubt, do not use it at all [19]

First cases of spontaneous UR were published by Feeney in 1956 with both cases receiving 5 units of oxytocin [19].

Misoprostol (Cytotec®; Searle and Co, Chicago, IL) is a synthetic prostaglandin E1 (PGE1) analog. Owing to its uterotonic effect, it has been used as an abortifacient [147], for cervical ripening (placed in posterior vaginal fornix), for labor induction, and for the treatment of postpartum hemorrhage due to uterine atony [148]. UR with misoprostol induction has been reported in the English language literature in 20 instances up to 2001. Seven ruptures occurred in the unscarred uterus, whereas 13 cases had CS scars (see Sect. 16.4.1.8) [108]. In many instances, factors such as previous dilatation and curettage, fetal macrosomia, external cephalic version, multiparity, shoulder dystocia, or oxytocin use might have contributed to the rupture. Misoprostol was used in these cases in a dose of 25–100 µg or even 600 µg every 3–6 h with a maximum of four doses. In a meta-analysis, an odds ratio of 2.7 for tachysystole with misoprostol compared to other medications used for labor induction was observed [149].

PGE_2 (dinoprostone) is a potent oxytocic agent, and rupture of the unscarred uterus has been reported with vaginal and intracervical applications [25, 68], in doses up to 6 mIU/min. PGE_2 should be used with caution particularly in multiparous patients and in combination with oxytocin. Uterine hyperstimulation was not observed, and rupture occurred more than 4 h after administration [10].

16.4.2.2 Assisted Vaginal Delivery

The rupture was encountered after vacuum-assisted vaginal delivery. Application of external force in the second stage of labor [9], vacuum forceps, and breech extraction are all possible causes of UR [68]. Midforceps delivery and breech version extraction have been implicated as potential causes of UR [150]. Whether or not the manipulation causes the rupture is unclear.

16.4.2.3 Parity, Age, and Race

> *High multiparity carries with it certain inherent risks … it can be very unforgiving of any carelessness, incapacity or neglect.*
>
> John Kevin Feeney, 1935

The high parity, first observed by John Kevin Feeney (professor of gynecology and obstetrics in University College Dublin and master of the Coombe Hospital in Dublin) in 1953, is recognized as a major risk factor of spontaneous UR in an unscarred uterus [19, 151]. The uterus may have been weakened by thinning and stretching of the muscle fibers during labor, especially with aging and repeated childbearing [10]. The mean parity at the time of rupture is 5–6 [152, 153]; some reported that 56–75.6% of URs occurred in women with a parity of between 1 and 4 and 38% with parity 5–9 [154, 155]. The problem with the precise influence of parity is due to the reports of cumulative incidence in women with scarred and unscarred uterus [38]. Some claim that the incidence is rising till the third delivery and then decreasing [38]. Grand multiparity predisposes to malpresentation and unstable lie, a significant risk factor for ruptured uterus [58, 156]. Grand multiparas attended antenatal clinics sparsely (due to heavy domestic commitments), and, consequently, malpresentations are diagnosed late, during labor. Nevertheless, recent evidence sug-

gests that with proper antenatal care, modern obstetrics, and advanced neonatal services, there is no difference in outcome between grand multiparous women and women with low parity [157], with only 0.005% of UR among 39,529 multigravidas who had no previous uterine scar [62]. Uterine overdistention due to the presence of twin pregnancy was not proven to be the risk factor. Fetal weight in singleton pregnancy is a risk only when it contributes to cephalopelvic disproportion [36]. Age and parity are interrelated risk factors.

> Women older than 35 and women having their fifth or later birth are at greatest risk for spontaneous uterine rupture.

In this risk group, the importance of fertility regulation and contraception usage is obvious [36]. Others state the peak incidence in the 26–35-year age range [154], while one Nigerian study showed peak incidence in 25–29 age group. Probably, it is related to reproductive age and life span in developing countries with a significantly lower incidence of older parturient women. Unfortunately, these two factors are prominent features in obstetric practice in Qatar where repeated pregnancies continue into middle age. More than half (56.9%) of URs were grand multiparas (para 5 or more), and 39% were over 35 years of age. These findings suggest some additional risk factors that warrant consideration. Other etiological factors classically recognized as contributing to a rupture of the unscarred uterus are presented in the Table 16.1. Connective tissue diseases [158] may also induce UR. In some cases, the rupture of the gravid uterus has no obvious cause even before labor [11, 159].

A major factor for UR is obstructed labor. Black African women have a high incidence of contracted pelvis [160].

An unscarred prelabor primigravid uterus can show a very thin uterine wall, compatible with incomplete UR, without apparent etiological or risk factors. There have been 36 [161] and 22 [162, 163] cases of primigravid URs found over last 65 years (1946–2013). Of 21 cases found by Matsubara et al., 15 were reported in Nepal [164], with all ruptures occurring after labor duration of more than 48 h and 12 having received no antenatal care. Of all these 58 (36 + 21 + 1) cases, 55 had some discernible etiological or risk factors for rupture, including a past history of uterine surgery, congenital uterine anomaly, adherent placenta, labor, or oxytocin and/or prostaglandin use [158, 161, 163]. The etiological factors were described as indiscernible in the remaining two [165, 166], while in one there was a history of curettage [162], but without the evidence being a cause.

16.4.2.4 Congenital Uterine Anomalies

Congenital uterine anomalies affect approximately 1/200 women [167]. In such cases, the walls of the abnormal uteri tend to become abnormally thin as pregnancies advance, and the thickness can be inconsistent over different aspects of the myometrium [168] predisposing it to rupture (Fig. 16.6). The reported incidence of UR in women with congenitally malformed uteri is 8% compared to 0.61% in those with normal uteri who were attempting VBAC [169]. Cases of UR in the women with uterine anomalies involved labor induction with prostaglandin E2. In contrast, a study of 165 patients with Müllerian duct anomalies who underwent spontaneous labor after one prior CS reported no cases of UR [170]. Of note, in this study, 36% had only a

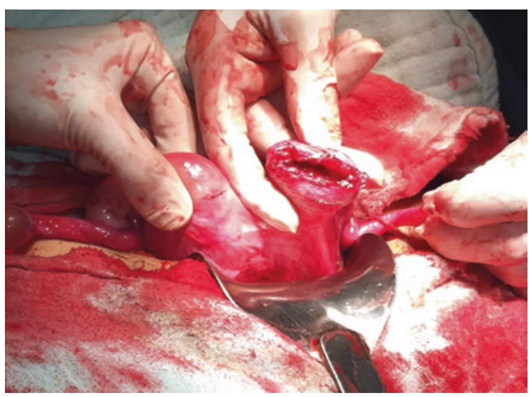

Fig. 16.6 Fundal uterine rupture in the left part of the bicornuate uterus in a 12-week pregnancy. Reproduced from [171] under the CC Attribution License

minor uterine anomaly (arcuate or septate uterus), and 64% had a major uterine anomaly (unicornuate, didelphys, or bicornuate uterus). Moreover, only 6% with Müllerian duct anomalies underwent induction of labor.

Rudimentary Horn

See Chap. 15.

16.4.2.5 Uterine Sacculation

A thin uterine wall, as a result of uterine sacculation [172, 173], may induce UR. Uterine sacculation is defined as a transitory pouch or saclike structure developing from a portion of the gravid uterus [172]. The typical form of sacculation results from an incarcerated retroverted uterus [172, 173]. A ventrally located cervical ostium and vagina may cause physicians to suspect this diagnosis. In this condition, the anterior uterine wall becomes stretched and thinned. Other conditions, such as previous surgery, a primary myometrial defect, uterine malformation, or placental abnormalities, are listed as possible causes of uterine sacculation [172].

16.4.2.6 Uterine Diverticulum

The diverticulum can result from a developmental malformation (true diverticulum) or weakening of the uterine wall from prior uterine surgery (iatrogenic or secondary diverticulum) [174]. A uterine diverticulum is frequently misunderstood and reported as uterine sacculation [174]. Uterine sacculation, on the other hand, is typically a larger outpouching that contracts after delivery. It occurs during pregnancy as the uterus is distended by the destruction of the uterine wall by trophoblastic tissue [174]. The hypothesis for its development is that abnormal development of the paramesonephric duct may cause a congenital uterine deformity, leading to a formation of the diverticulum [175]. Uterine diverticulum has a narrow connection with the uterine cavity and a thicker wall than uterine sacculation [174]. While uterine sacculation is usually observed during pregnancy [172], diverticulum is usually detected in nonpregnant women. Uterine diverticula as complications during pregnancy are rare. If asymptomatic diverticulum in pregnancy is found, it is reasonable to perform elective CS prior to uterine contractions and labor. Extreme caution is needed because there are cases of UR prior uterine contractions as a start of labor [174, 176]. Also, if a gestational sac is implanted in a diverticulum [175], there is a significant risk of UR and other obstetric complications, and the termination of pregnancy is recommended.

16.4.2.7 Genetic Susceptibility for Rupture

Loeys–Dietz syndrome is a syndrome caused by heterozygous mutations in the genes encoding type I or II transforming growth factor-β receptor (TGF-βR1/2). The obstetric manifestations are a risk of rupture of the gravid uterus and the arteries, either during pregnancy or in the immediate postpartum period, and damage to the vagina, the perineum, and the colon [177].

16.4.2.8 Antenatal Care

The prenatal care in some undeveloped countries such as Yemen or Uganda is very poor. Only 44% of pregnant women had ever been to any prenatal clinic, with the frequency of visits during a pregnancy ranging from one to four. Women visit antenatal clinic mostly when they encounter a complication and very rarely for a routine antenatal care (13%). In Yemen, 56% of pregnant women have never had any antenatal care. Home delivery is still common. About 78% of women deliver at home, 16% at state hospitals, and about 5% at private hospitals. The home deliveries are usually attended by midwives with minimal training or relatives who have had some experience of labor. Some of the women will still deliver at home completely alone [36]. In Uganda, the majority (67%) of the women did not attend antenatal care [17].

16.4.2.9 Epidural Anesthesia

Epidural anesthesia has also been linked to UR; however, in those patients with UR, the incidence of epidural use is small and ranges 6–21% [55, 178, 179].

16.4.2.10 Uterine Fibroids

Fibroids are associated with numerous pregnancy complications (see Chap. 18), including pain, miscarriage, premature labor and delivery, malpresentation, and placental abruption [180–182]. It is thought that there is a 10–40% incidence of complications in this group [183]. Fortunately, there is only one case of ruptured uterine fibroid causing UR during labor (Fig. 16.7).

16.4.3 Operative Procedure

16.4.3.1 Uterine Myomectomy

Most URs with myomectomy scars have occurred during the third trimester of pregnancy or during labor [78, 185] with several cases during the second trimester [75, 186]. Studies claim UR rate of 3–4% in women who had scars from a previous myomectomy—open or laparoscopic [78, 187]. Such reports do not often delineate the factors that were deemed important for assessing the risk of subsequent UR (e.g., number, size, and locations of leiomyomas, number and locations of uterine incisions, entry of the uterine cavity, type of closure technique). Another important issue is the site of UR in comparison with the site of myomectomy scar. If that is included in the analysis, risk is significantly lower and is around 0.26–1% [78, 185].

Fig. 16.7 Ruptured uterine fibroid at the time of Cesarean section. Reproduced with permission from [184]

Therefore, the rarity of spontaneous UR raises the issue of whether the URs at sites that were not coincident with previous myomectomy scars were attributable to the previous myomectomies. Others reported no pregnancy-related URs in women who previously underwent laparoscopic or transabdominal myomectomy [188, 189]. However, the number of patients who were allowed to labor was low, and a high percentage of deliveries were by scheduled CS (80, 79, 75, and 65%, respectively). UR has been reported to occur as late as 8 years after laparoscopic myomectomy [190]. This finding suggests that additional investigations with long-term follow-up are needed. This should be compared to the fact that pregnancy and vaginal delivery are safe 18 months after CS (see Sect. 16.4.1.11).

It has previously been recommended that if the fibroids had been numerous and deeply placed, if the endometrium had been opened, if accurate apposition of the wound edges and hemostasis had not been secured, if convalescence had been complicated by fever, and if the placenta has been implanted (on ultrasound examination) upon an endometrial scar, then elective CS should be performed [19].

16.4.3.2 Medical Abortion

Medical abortion was started in the late 1980s, becoming more widely used in the late 1990s with mifepristone and misoprostol being the most used. It came as an alternative for the dilatation and curettage which caused more complications, resulting in 50,000–100,000 maternal deaths every year [191, 192]. No randomized controlled trial has been powerful enough to properly compare medical and surgical abortions in relation to the possible adverse effects. Misoprostol (partial progesterone receptor agonist which also antagonizes cortisol action competitively on the receptor level) alone for the termination of pregnancy was described in 1994. It has been used widely in the normal uterus [191, 192]. The absence of previously reported cases of gemeprost-associated UR may reflect the rarity of this method of pregnancy termination in the second trimester. Initially, higher doses were administered, and the conclusion

was that smaller doses may lessen the risk of uterine hypertonus and decrease the risk of UR [193]. The additional risk factor in such cases is scarred uterus [194–196], but there are even cases with the unscarred uterus [108, 197]. The systematic review from 2009 found seven times higher incidence of UR of scarred uterus (0.28%) in comparison with the unscarred uterus (0.04%), but authors found the incidence acceptable [198]. UR in an unscarred uterus is possibly related to the dose, dose interval, gestation, and parity. Based upon pharmacokinetics of misoprostol, a dosage interval of 6 h is common (range 3–12 h) [199]. UR occurred in one case with lower accumulated dose of misoprostol (1200 μg/30 h) than in some reported regimens (2400 μg/24 h) [199]. There is even a case of spontaneous UR of the unscarred uterus in the first trimester using mifepristone/misoprostol for medical termination of pregnancy [200]. Corticosteroid therapy is listed as a contraindication to mifepristone (but not misoprostol), possibly because of its glucocorticoid antagonistic effect. Whether prolonged corticosteroid therapy can result in a weakened myometrium susceptible to rupture remains to be determined. The incidence of UR among women with a prior CS during second-trimester pregnancy termination with prostaglandin E_2 or oxytocin is 3.8% [201]. The risk is even higher when oxytocin is used with prostaglandins [202]. There was no set regimen protocol for intravaginal misoprostol in second-trimester pregnancy termination. Mostly the initial dose was 400 μg repeated every 4–6 h, up to a maximum of 1200–1600 μg per 24 h. Some studies have augmented misoprostol with either oxytocin or mifepristone [194, 197, 201]. Recently, FIGO has recommended the regimen protocol for second-trimester pregnancy termination with 100–200 μg intravaginal misoprostol, repeated 6 h till maximum four doses/24 h [202], and its use should be with care in a previously scarred uterus. Four cases of rupture of an unscarred uterus in the second trimester following MTOP were found. Only two of these cases used mifepristone and misoprostol [203]. The other women found do not follow the MTOP protocol but contain information relevant to this case. The first was an MTOP using mifepristone and gemeprost. The rupture was found by ultrasound scan the morning after commencing prostaglandins [204]. The second case was a grand multiparous patient [196]. The UR was found by ultrasound scan following one dose of misoprostol (200 μg) followed by oxytocin 12 h later. Although high doses of prostaglandins are a known risk factor, the above two women were treated for over 24 h, raising the possibility that duration of prostaglandin treatment is a risk factor. Other agents, such as ethacridine lactate, have been linked to UR, although this is very rare and the case was relating to the second trimester [205]. Cases of UR have been reported involving small doses of misoprostol. One case involved an endocervical rupture in the second trimester following two doses [206]. Another was a scarred uterus [207], and the similar case was a first-trimester rupture following one dose of misoprostol both in preparation for surgical termination [208].

There is no evidence that pretreatment with mifepristone might increase the chance of UR. It is thought that the chance might actually be reduced as mifepristone increases cervical compliance; however, as it increases uterine sensitivity to the action of exogenous prostaglandins [204], the risk benefit is not known. Previous CS is thought to be a risk factor for UR. One trial of second-trimester abortion using misoprostol in 720 women with one or more previous CS has been carried out and concluded that the use of misoprostol was not associated with an excess of complications compared with women with unscarred uteri [209].

16.4.3.3 Uterine Curettage

Uterine perforation rate of 19.8/1000 at the time of dilatation and curettage when laparoscopy is used to evaluate the uterine fundus is reported [163]. Most cases are asymptomatic and a scar can be found on a possible future intra-abdominal operation. Unfortunately, a scar due to uncomplicated curettage that is a risk for UR could not be detected during regular pregnancy ultrasound examinations as a uterine wall defect.

Prelabor UR in primigravid women was identified in 24 cases up to 2011. In almost half of them, partial wall defect was the principal recognizable risk factor before the onset of labor. It is interesting to note that 52% of women with specific available information had a history of

infertility. A possible explanation could be that infertile patients more frequently undergo diagnostic/operative procedures on their uterus during diagnostic investigation or treatment resulting in a likelihood of iatrogenic damage [210].

16.4.3.4 Salpingectomy

Location of the ectopic pregnancy, type and quality of suture material used, suturing technique, the use of mono- or bipolar electrocautery, and the gynecologist's experience constitute important factors that influence final outcomes after laparoscopic Fallopian tube resection [211, 212].

In order to decrease the risk of long-term complications from a ruptured tubal pregnancy localized near the cornual region, use of additional reinforcing sutures during laparoscopy appears to be a more appropriate management than electrosurgery alone since cautery-induced thermal injury may compromise the myometrial tissue [213]. However, additional sutures in the cornual region may be associated with a risk of myometrial ischemia; therefore, extensive suturing should be avoided. For unruptured tubal pregnancy, conservative therapy with methotrexate and laparoscopic salpingostomy are currently the methods of the first choice (see Sect. 15.1.7.2) that can prevent serious complications in subsequent gestations [214].

Apart from the surgical approach, the time period between surgical removal of a Fallopian tube and conception seems to be very important, given that it was <12 months in 67% of the analyzed URs in the group of non-ectopic pregnancies. Interstitial pregnancy was the cause in all cases. Based on the available data, however, it is not possible to determine with a high degree of certainty the safe interval between conception and salpingectomy, and the risk of UR during subsequent pregnancy cannot be completely excluded after several years [215].

16.4.3.5 Uterine Artery Embolization

Except for uterine artery embolization, described cases with UR had additional risk factors for which the uterine artery embolization was indicated. Most include (resected) uterine myomas and/or abnormal placentation during pregnancy with UR [216–218].

16.5 Prevention of Uterine Rupture

16.5.1 Scarred Uterus

The most direct prevention strategy for minimizing the risk of pregnancy-related UR after CS is to minimize the number of patients who are at highest risk. The salient variable that must be defined in this regard is the threshold for what is considered a tolerable risk. Although this choice is arbitrary, safety threshold is chosen as 0.5% (1/200); therefore, the categories of patients that exceed this critical value are those with previous:

- Multiple CS
- Classic midline CS
- Low-vertical CS
- Low-transverse CS with a single-layer hysterotomy closure
- CS with an interdelivery interval of <2 years
- Low-transverse CS with a congenitally abnormal uterus
- CS without a previous history of a successful vaginal birth
- CS with either labor induction or augmentation
- CS in a woman carrying a macrosomic fetus weighing >4000 g
- Uterine myomectomy

Accurate prediction of UR would be extremely valuable, as it would allow women at low risk to proceed with a TOL, whereas women at high risk for UR could undergo a planned CS. Thinning in the lower uterine segment measured by ultrasonography is a predictor of UR either complete rupture or scar dehiscence at birth, during TOLAC. A full lower uterine segment thickness cutoff of 3.1–5.1 mm and a myometrium thickness cutoff of 2.1–4.0 mm provided a strong negative predictive value for the occurrence of a defect during TOLAC. A myometrium thickness cutoff between 0.6 and 2.0 mm provided a strong positive predictive value for the occurrence of a defect [219]. Interobserver agreement is that lower uterine segment thickness should be measured by transvaginal sonography [220].

16.6 Clinical Presentation

The prevalence of Müllerian duct malformations in the general population and in the population of fertile women is estimated to be 4.3% and in the infertile patients approximately 25%. Septate uterus is the commonest anomaly with a mean incidence of approximately 35% followed by bicornuate uterus which is approximately 25% and arcuate uterus approximately 20% [221]. These malformations remain asymptomatic till the patient reaches reproductive age. Such anomalies are reported to result in increased rate of infertility, miscarriage, recurrent pregnancy loss, preterm labor, and other obstetric complications. Clinical presentation varies from being asymptomatic to vague complaints of mild lower abdominal pain with gastrointestinal upset and finally to its severest form of acute abdomen with hemorrhagic shock. Women who have a noncommunicating uterine horn may present after menarche with progressive abdominal pain caused by hematometra, hematosalpinx, and endometriosis. However, many women remain asymptomatic.

16.6.1 Symptoms and Signs

The symptoms and signs of UR largely depend on [19]:

- Time of occurrence (pregnancy, early or late labor)
- Cause
- Duration
- Site
- Type
- Degree
- Extent
- Amount of intraperitoneal spill
- Size of the blood vessels involved
- Complete or partial extrusion of the fetus and placenta
- Intensity of retraction of the uterine muscle

An ordinary variety of UR in which more obvious signs and symptoms develop over a period of a few hours have been reported back in the 1890s [4]. Sudden, severe, shearing abdominal pain with the absence of fetal heart sounds and cessation of uterine contractions in conjunction with vaginal bleeding and shock is a classical presentation. Overall, only 45% of cases reviewed have classical symptoms and signs of UR [34, 40, 49, 150, 155, 222–225].

16.6.1.1 Pregnancy

Common symptoms and signs are abdominal pain and tenderness; shock (faintness, pallor, and tachycardia); vaginal bleeding; fetal distress, manifested by fetal bradycardia and the absence of fetal movement; undetectable fetal heartbeat; palpable fetal body parts; cessation of contractions; and signs of intraperitoneal bleeding. Severe abdominal pain is present in 14% of patients, shock in 10–21.3%, bleeding in 16.8%, the disappearance of fetal heart sounds in 8.9%, and cessation of contractions in 5.6% [71, 224]. Less commonly associated with UR are an epigastric pain, shoulder pain (right sided or bilateral), abdominal distention and paralytic ileus, hematuria due to rupture extension to the bladder, hypertonic uterus, altered uterine contour, and fluid thrill.

16.6.1.2 Labor and Postpartum

Rupture of the uterus during labor is associated with cessation of labor pain, the recession of presenting fetal body parts, cervical lacerations, and vaginally palpable uterine defect. One of the pathognomonic signs of constriction-ring dystocia is that, despite a painful colicky type of contraction originating and felt in the upper part of the uterus, no impulse of descent or pressure is imparted to the presenting fetal head below. Downward contractile impulse is apparently cut off by the gap in the continuity of the muscle fibers at the site of rupture. After rupture, the uterus continues to contract above, but the fetal head below remained immobile to the examining finger during a contraction [19]. This phenomenon partly depends on the degree and extension of the rupture and associated partial or complete expulsion of the fetus in the peritoneal cavity.

The most common sign is the sudden appearance of fetal distress during labor. In up to 81% of patients with UR during labor have evidence of fetal distress prior to the onset of bleeding or abdominal pain [179] and fetal heart abnormalities in 43.5% [52]. The observation of sudden fetal heart irregularity in laboring women should be taken as a potential sign of danger [63].

With other symptoms and signs, postpartum bleeding is present in 24%, while postpartum abdominal pain, distention, and ileus are present in 14% [71]. A large blood clot evacuated along with spontaneous exit of the placenta, especially in patients on uterotonics or prostaglandins for induction of labor, should raise the suspicion of UR [108]. Another suspicious sign is blood-stained liquor after rupture of membranes [184].

16.6.1.3 Scarred Uterus

The symptoms and signs of UR in patients with scarred uterus differ from patients without a uterine scar [223]. UR at the site of a previous uterine scar is typically less violent and less dramatic than a spontaneous or traumatic rupture because of their relatively reduced vascularity. The most common sign in women with the previous uterine scar is lower abdominal tenderness. In women without a scar, the shock is the most common sign, followed by uterine bleeding, severe abdominal pain, and easily palpable fetal parts. Severe abdominal pain is common to both groups of women with and without a uterine scar.

16.6.1.4 Incomplete and Silent Rupture

Quiet, silent, or *occult rupture*, at first, occurs without the symptoms and signs that are ordinarily associated with UR. Diagnosis may, therefore, be difficult or unduly delayed, and unless the possibility of rupture is entertained, it may be missed. In quiet rupture, there is the uncomplaining multipara in labor or the patient whose CS scar is stretching and finally yields in either pregnancy or labor. Nothing dramatic happens, but an increase in the pulse rate, pallor, and perhaps slight vaginal bleeding, and the patient complains of some pain that is present. Contractions may continue unaltered, but the cervix fails to dilate further—a very important sign [19]. Uterine tenderness on internal examination is present [226]. UR as the incidental finding is present in 4.5% [224]. There are cases that presented as puerperal sepsis, which, at the end, is shown to be unrecognized UR.

Silent antepartum UR is usually associated with a previous uterine scar, produced by CS, myomectomy, or perforation of the uterus at the time of curettage. Spontaneous silent rupture of the intact uterus is exceptionally rare [159, 166, 226, 227] in the antenatal period, without predilection of UR location. It is found in women of high parity.

16.6.1.5 Delayed Presentation

Delayed presentation with abdominal pain and minimal or absent other symptoms and signs is possible if the uterine perforation is "covered." The rupture site may be covered from the outside by the small intestine [228] or from the inside by fetal legs [229] preventing acute massive bleeding. Therefore, vital signs and laboratory data could be stable. Covering by the small intestine may also prevent amniotic rupture or amniotic cavity protrusion, which may explain the initial absence of a fetal heart rate pattern indicative of cord troubles (Fig. 16.8).

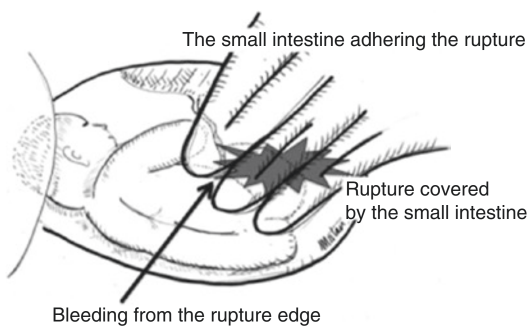

Fig. 16.8 Schematic diagram of the laparotomy findings. The uterine rupture was not initially discernible. Bleeding was observed from the rupture edge (*arrow*). The small intestine tightly adhered to the anterior uterine wall over the uterine rupture. After separating the small intestine, uterine rupture became evident. Amniotic membrane beneath the rupture site remained intact. Reproduced with permission from [228]

Another delayed presentation is found during early postpartum. The condition is not suspected or diagnosed until the patient has become established upon a slow but progressive postpartum bleeding. The UR which does not cause symptoms until the early postpartum period is of special importance, because bleeding, traumatic in origin, may be attributed to atony of the uterus and collapse to so-called obstetrical shock [19].

16.6.1.6 Spinal Anesthesia

There has been concern that the use of epidural analgesia may mask clinical symptoms (mostly abdominal pain) causing delayed diagnosis of UR [26]. The most common sign of UR is nonreassuring fetal heart rate pattern with variable deceleration [81]. Other findings are more variable and include abdominal pain, vaginal bleeding, and hypovolemia. Epidural analgesia rarely masks the signs and symptoms of UR, and in fact, sudden development of "breakthrough pain" under epidural analgesia may improve the specificity of abdominal pain as a symptom of UR in patients attempting vaginal birth after previous uterine surgery [81].

16.6.2 Physical Examination

A physical examination reveals tenderness in the middle of the lower abdomen with or without guarding. Vaginal bleeding can be present. Blood pressure depends on the rate of uterine bleeding, and the patient can be hypotensive with increased pulse rate. There is a recommendation that *clinicians should consider the diagnosis of uterine rupture when a patient presents with abdominal pain, even without evidence of hypovolemia, vaginal bleeding, contractions, or fetal compromise* [228, 229]. Shoulder pain (*Kehr's sign*) is a valuable sign of intraperitoneal blood in the subdiaphragmatic region. Even a small amount can cause this symptom, but it is important to realize that it may be 24 h or longer after the bleeding has occurred before blood will track up under the diaphragm, and some cases of acute massive intraperitoneal bleeding may not initially have shoulder pain. Sooner or later, however, shoulder pain will usually appear, and it is in the doubtful cases with a slow leak of blood into the peritoneal cavity over a period of 2 or 3 days that such referred pain is of great diagnostic value.

If there is sufficient cervical dilatation, the vaginal examination may reveal intestinal loops or parts of the greater omentum in the uterine cavity or a defect of the (lower) uterine segment can be revealed [108]. There is also considerable abdominal distention with dyspnea, caused by the compression of the thoracic cavity. Postpartum fever ≥38 °C after CS is associated with an increased risk of UR during a subsequent trial of labor [230]. Antepartum hemorrhage (APH) often indicates UR [29] and may occur in association with shoulder tip pain due to hemoperitoneum. APH was documented in 33% of posterior URs [28]. With posterior UR, bleeding may be concealed, where signs of hypovolemia develop, with a large, concealed hemoperitoneum [25, 26]. It should be kept in mind that maternal pulse and blood pressure could remain within normal limits despite massive UR, demonstrating the potentially misleading capacity for compensation in an otherwise fit patient. In 33% of posterior URs, women reported persistent abdominal pain [25, 28]. If the fetus is partly or completely outside the ruptured uterus, especially if the rupture is on the anterior wall, hard mass can be palpated [8].

16.7 Diagnosis

> *It is a worthy subject of an obstetrical truism—that is, if a multiparous patient, in pregnancy, in labour, or in the early postpartum period, should develop constitutional or local (abdomino-pelvic) signs and symptoms for which there is no ready explanation, then rupture of the uterus should at least be suspected.*
>
> John Kevin Feeney, 1956

16.7.1 Laboratory Findings

Only 30% of patients are diagnosed with UR preoperatively [63, 154]. Laboratory findings should include hemoglobin which is lowered, and the exact value and dynamics of its decrease depend on the intensity of uterine wall bleeding. Suspicion of placenta accreta/percreta arises in the case of unexplained elevation of alpha-fetoprotein [231].

16.7.2 Abdominal Ultrasound

A transvaginal and transabdominal ultrasound should be performed to search direct and indirect findings of UR. Direct signs are thinned wall with bulging of fetal parts (Fig. 16.9) and visualization of the rupture. The fetus can be partly (Fig. 16.10) or completely out of the uterus (Fig. 16.11). Indirect signs are free peritoneal fluid (blood) especially in the pouch of Douglas, extraperitoneal hematoma, intrauterine blood, empty uterus, gestational sac above the uterus (Fig. 16.12), and large uterine mass with gas bubbles [8, 232, 233]. Congenital uterine anomalies or acquired uterine changes can be seen, adding suspicion about UR.

Fig. 16.9 An abdominal ultrasound image of the uterine wall and the fetal minor part. Small arrow indicates a thin uterine wall, which is slightly bulging. Beneath the thin uterine wall, a fetal minor part (*large arrow*) is visible, which was palpated as a hard mass through the abdomen. Reproduced from [8] under the CC BY 2.0

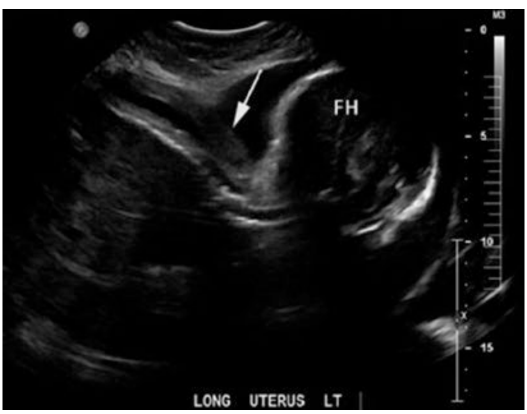

Fig. 16.10 Unrecognized edge of the uterine rupture (originally diagnosed as synechiae (*arrow*) due to the history of uterine curettage) and the fetal head (*FH*) already extruded through the uterine defect. Reproduced with permission from [162]

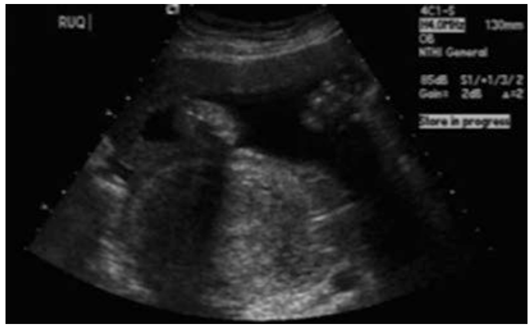

Fig. 16.11 Abdominal ultrasound demonstrating contracted uterus with fetal extremities and amniotic sac outside the uterus. Reproduced with permission from [232]

Fig. 16.12 Abdominal ultrasound demonstrating contracted uterus, endometrial stripe, and no intrauterine gestation, with the placental tissue above and bladder to the right. Reproduced with permission from [232]

16.7.3 Abdominal CT

Abdominal CT scan should be done in unequivocal cases such as intestinal adhesions over UR delaying diagnosis. It is seen as a focal disruption of the myometrium along with hemoperitoneum (Fig. 16.13). Other signs (see Sect. 16.7.2) such as fetal parts or hemoperitoneum outside of the uterus can be seen (Figs. 16.14, 16.15, 16.16, and 16.17).

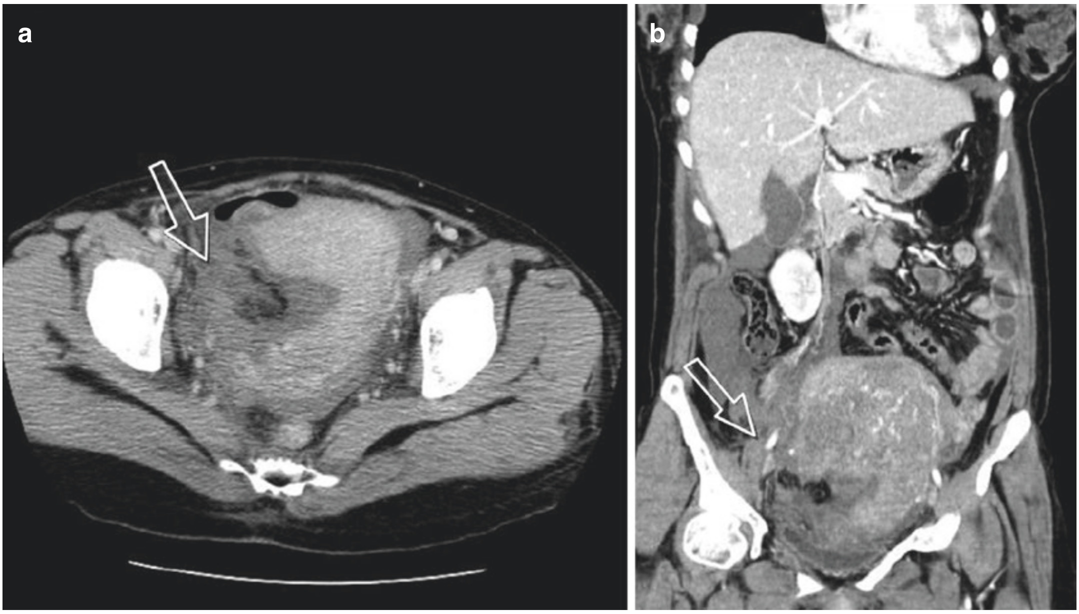

Fig. 16.13 The abdominopelvic CT scan of partial uterine rupture. Axial (**a**) and coronary image (**b**) of the hemoperitoneum with a muscle defect with invagination of the omental fat (*arrow*) in the right lower portion of the postpartum uterus. This suggests uterine rupture with hemoperitoneum. Reproduced with permission from [234]

Fig. 16.14 Contrast CT scan of the abdomen and pelvis showing a defect in the anterior wall of the uterus (*arrow*) and fluid collection with wall enhancement and adjacent fluid collection 2 weeks after elective Cesarean section. Reproduced with permission from [235]

Fig. 16.15 Axial CT scan of the abdomen (the same patient as in Fig. 16.14) showing the measurement of fluid collection anterior to the uterus (*arrow*). Reproduced with permission from [235]

16.7.4 Abdominal MRI

Diagnosis by ultrasound relies on nonspecific, secondary signs such as the presence of free fluid or hematoma formation, while MRI allows the visualization of the uterine wall defect or tear itself resulting in a more definitive diagnosis [237]. In comparison to ultrasound, MRI is less operator dependent and provides a more comprehensive study with a larger field of view. MRI

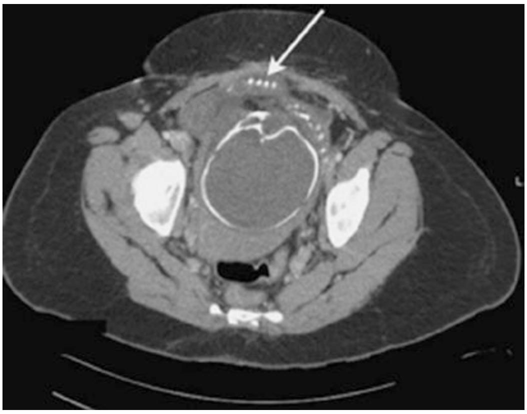

Fig. 16.16 A 34-year-old woman with seven previous Cesarean deliveries presented at 32 weeks. The CT scan revealed a fetal hand protruding through the lower uterine segment (*arrow*). Reproduced with permission from [236]

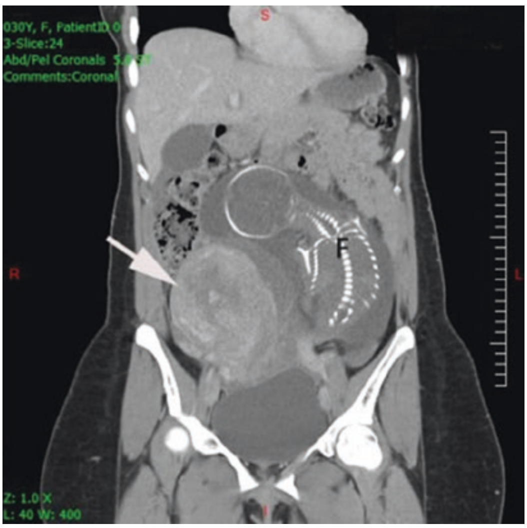

Fig. 16.17 Abdominal CT after the uterine rupture. Arrow denotes the empty uterus with fetus (*F*) outside of the uterus. Reproduced with permission from [162]

may also be less uncomfortable for the patient with a tender abdomen.

The MRI appearance consists of a focal myometrial defect (1) which may be filled with hematoma and an associated hemoperitoneum (Fig. 16.18) or (2) protruding amniotic cavity (Fig. 16.19). UR is a surgical emergency, and MRI should only be considered when the diagnosis is inconclusive and the patient is hemodynamically stable [238].

In cases of scar dehiscence, an extensive fluid collection with air bubbles in the bladder flap as a

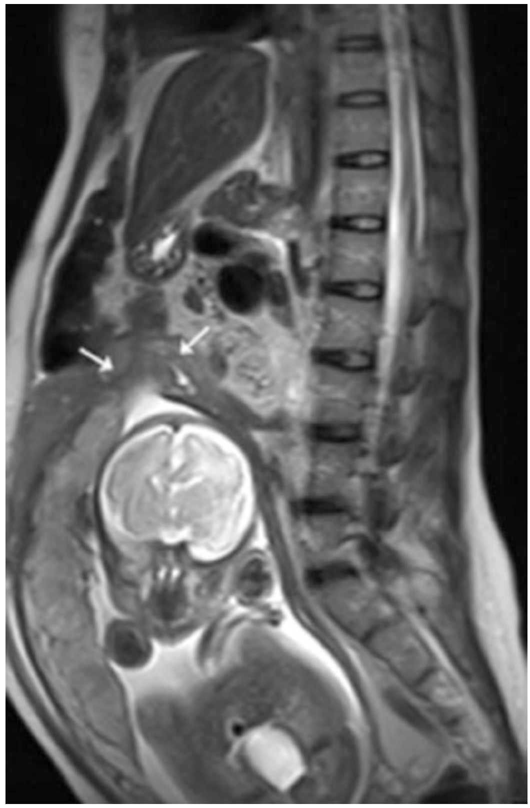

Fig. 16.18 A 35-year-old female in the third trimester with prior Cesarean delivery. Sagittal T2-weighted image shows a focal disruption at the fundus of the uterus (*arrows*) with associated hematoma. No part of the fetus protruded into the abdominal cavity. Reproduced with permission from [239]

sign of local infection can be seen. The differential diagnosis should consider bladder flap hematoma, endometritis, and normal CS incision changes, which are better depicted with MRI than CT. MRI may provide a preoperative diagnosis of uterine sacculation [173] or uterine diverticulum [174].

16.7.5 Uterine Tone Monitoring

CTG abnormalities are associated with 55–87% of URs [241]. Other recognized signs of UR include loss of station of presenting part and new inefficient contractility [242]. Uterine tone monitoring is mandatory in patients with clinical suspicion of UR.

External monitoring (external tocodynamometer) demonstrates the classic sign of complete

loss of uterine tone. In contrast, internal monitoring (internal pressure transducer) demonstrated an increase in uterine resting tone. Both techniques reveal a stepwise gradual decrease in contraction amplitude followed by a sudden onset of profound and prolonged fetal bradycardia in patients with rupture of an unscarred uterus at term—*staircase sign* (Fig. 16.20). When internal monitoring was used, the intrauterine pressure catheter did not show a complete loss of resting tone (Fig. 16.21). In general, internal monitoring has better sensitivity for the detection of both fetal heart rate and uterine contraction, consistent with the published reports of the persistence of uterine contraction and increased resting tone in cases of rupture monitored by intrauterine catheter—findings that were not observed with external monitoring [10, 179]. However, few papers in the literature actually documented the type of uterine monitoring used. Furthermore, the uterine contraction pattern may differ depending upon the presence or absence of a uterine scar or with the site and direction of rupture. Bradycardia is the most common fetal heart rate abnormality seen in UR [179, 243] and may occur as a result of cord compression within the UR, loss of uterine perfusion, or placental abruption. This staircase pattern appears to be a unique combination of fetal heart rate pattern and uterine contraction pattern that may be of value in diagnosing UR. Fetal bradycardia starts right after or several minutes after staircase sign [244]. Intermittent fetal heart tone auscultation should be performed while the patient is off continuous monitoring and should be standard.

Fig. 16.19 Abdominal MRI (T2WI, coronal section) of the pelvis revealed a bulging amniotic cavity protruding through the defect in the uterine wall (*arrows*). Neither peritoneal fluid nor hemoperitoneum was observed. Reproduced from [240] under the CC Attribution License

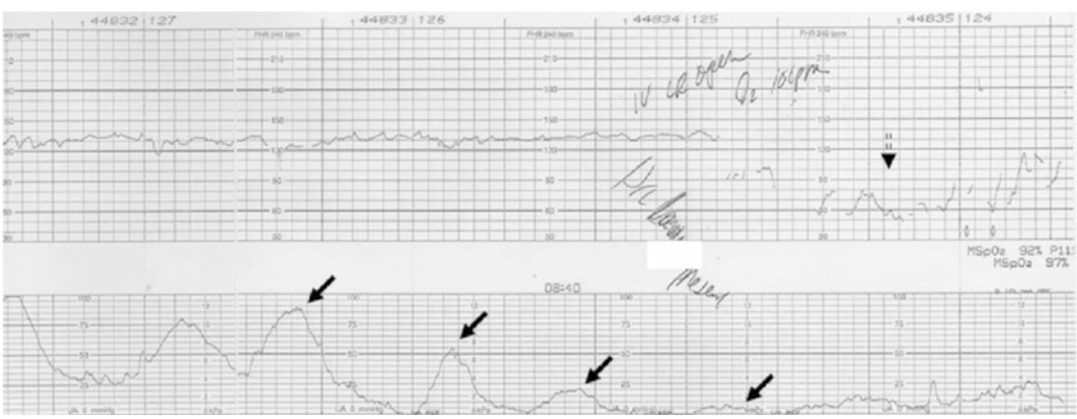

Fig. 16.20 Uterine contraction pattern during rupture of an unscarred uterus at term. External cardiotocography was used for the tracing. *Black arrows* show the gradual decrease of the amplitude of uterine contractions (*staircase sign*). *Black arrowhead* with dashed body shows prolonged fetal bradycardia. Reproduced with permission from [244]

Fig. 16.21 Uterine contraction pattern during term rupture of an unscarred uterus. Intrauterine pressure catheter was used for the tracing. *Black arrow* shows the gradual decrease of the amplitude of uterine contractions (*staircase sign*). *Black arrowheads* with dashed body show prolonged fetal bradycardia. *Gray arrow* shows increased resting tone. Reproduced with permission from [244]

16.8 Treatment

The patient with threatened UR should be examined gently but thoroughly, under an anesthesia, by a person experienced enough to carry out whichever method of treatment may be indicated. If UR is not diagnosed until after delivery, the method of treatment is determined by the extent of the laceration. In complete UR laparotomy is indicated; in partial UR a cautious trial of treatment by plugging from below may be employed.

16.8.1 Perioperative Management

Once a diagnosis of UR is established, the immediate stabilization of the mother and the delivery of the fetus are imperative. After securing the airway and adequate oxygen delivery, careful and immediate attention must be paid to correct hypovolemia. Patients should have multiple, preferably large-bore, intravenous catheters placed with vigorous fluid resuscitation. In a case of obvious complete and extensive rupture with extrusion of the fetus into the peritoneal cavity and with vaginal bleeding, ergometrine may be administered as an emergency measure in order to control bleeding from the rent and from the placental site while preparations for the laparotomy are being made.

The use of prophylactic antibiotics is controversial; some state that they have no value [11], while others recommend their use [36] because 23% had intraperitoneal sepsis at the time of laparotomy [69]. Partly it depends on the quantity of blood loss. Hypovolemic shock may lead to invasion of gram-negative bacteria from the ischemic bowel mucosa to the bloodstream, complicating the picture with endotoxemia and septic shock [245]. Hemorrhagic shock increases the incidence of wound infections. The majority of patients had mean blood loss of more than 2000 mL.

For other details see Chap. 21.

> At least 1000 mL of packed red blood cells or blood transfusions should be available [38, 71, 162].

16.8.2 Operative Treatment

The uniformly fatal termination in a very short space of time, of every case of rupture of the uterus that had come to my knowledge in the practice of my friends, or of my own, induced me seriously to reflect what could be done, or what might be rationally attempted, in these deplorable cases

William Jackson, 1845

Around 1845, maternal and fetal mortality was near 100%, and William Jackson (an anatomist and physiologist at the Medical Institution, Sheffield, UK) advocated surgical exploration when UR was suspected [146]. Despite this conclusion, in 1932, Mahfouz still urged conservative treatment whenever possible [246], but nowadays it is known that the key to successful treatment is early surgical intervention.

The time available for successful intervention after a frank uterine rupture and before the onset of major fetal morbidity is only **10–37 min** from the onset of fetal distress on the electronic fetal heart rate monitor [79, 101, 243].

After the fetus is successfully delivered, the type of surgical treatment should depend on the following factors:

- Type of uterine rupture
- Location of uterine rupture
- Extent of uterine rupture
- Degree of hemorrhage
- Condition of the mother
- Future childbearing

16.8.2.1 Suture Repair

Before the decision of the type of surgical management, it is important to define all locations of the rupture. Most ruptures are at the single site, but there are cases of both anterior and posterior ruptures (10.7%) or bladder and vaginal involvements (9% and 5%, respectively) [38]. Uterine bleeding is typically more profuse when the uterine tear is longitudinal rather than transverse. “Conservative surgical management” involving uterine suture repair (Figs. 16.22 and 16.23) should be reserved for women who have the following findings [71, 226]:

- Desire for future childbearing
- Low-transverse uterine rupture
- Fundal uterine rupture
- No extension to the broad ligament, cervix, or paracolpos
- Easily controllable uterine hemorrhage
- Good general condition
- No coagulopathy?

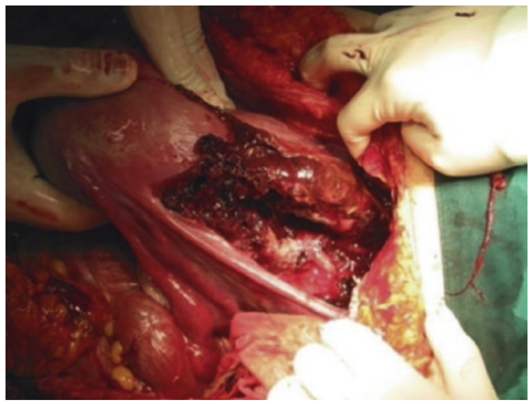

Fig. 16.23 The postpartum uterine rupture. The right aspect of the uterus is ruptured. The right round ligament and uterine artery are intact making suture repair possible. Reproduced with permission from [234]

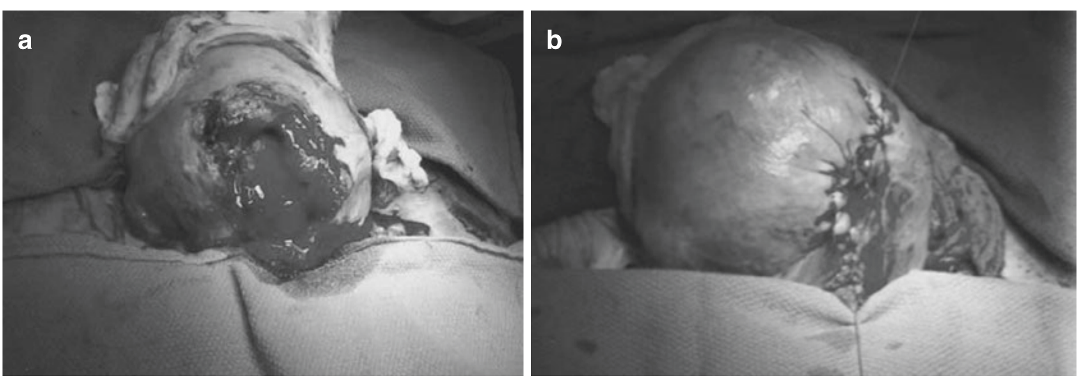

Fig. 16.22 (**a**) The ruptured and contracted uterus found during emergent exploration. (**b**) The line of uterine rupture, extending inferiorly from the left side of the previous lower-segment scar. Reproduced with permission from [232]

Suture repair is not contraindicated in the congenitally malformed uterus [171]. Repair of a UR is achieved in 13–74% of cases [32, 38, 55, 178, 179, 247]. Suture repair carries a recurrence risk of UR of 4–19% at a subsequent pregnancy [13, 248, 249]. Therefore, it is recommended that women with a previous suture repair of UR undergo an elective CS as soon as fetal lung maturity is demonstrated [250] or the patient is hospitalized and monitored until 37 weeks and then CS performed [251]. Recommendations are not strong because there are no prospective studies.

The type and location of UR dictate the type of uterine repair. If the lower anterior uterine wall is ruptured, then primary repair is accompanied by hemostatic techniques such as hypogastric artery ligation [71]. The percentage of patients with simple repair of the uterus is significantly higher in the scarred uterus group (90.2%) when compared to the unscarred uterus group (57.5%). Hysterectomy is performed in 25% of the patients with a previously unscarred uterus, which is significantly higher than the 9.8% in patients with scarred uterus [59]. Types of sutures and suturing technique are discussed in Sect. 16.4.1.12. There are several cases with suture line reinforcement with adhesives (fleece-coated fibrin glue) [144, 252] or patches (Vicryl mesh, Goretex mesh) [253, 254].

However, if an obvious cause is detected during surgery, the patient is multiparous, and no future pregnancy is desired, or it is suspected that future conception may be dangerous, suture repair of the rupture with tubal ligation for sterilization could be performed instead of hysterectomy [70, 255].

The extent of endometrial activity within the horn and the degree of separation to the other side are important factors that influence management, but as yet these factors are not included in any formal classification system. If the rupture is due to rudimentary horn pregnancy, it is difficult or impossible to separate the placenta from the rudimentary horn. In such cases, the rudimentary horn of the uterus along with the placenta should be excised (see Chap. 15) [256] or subtotal hysterectomy (see Sect. 16.8.2.2) performed.

If there are risk factors for UR present, some authors, to prevent the development of UR, recommend a continuous infusion of a tocolysis (Fig. 16.24) [144].

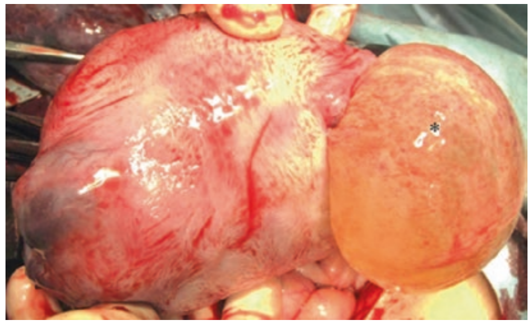

Fig. 16.24 Intraoperative appearance of the uterine fundus before placenta removal. A uterine perforation was located at the right corneal area, and the amniotic sac (*asterisk*) was prolapsed. Reproduced from [240] under the CC Attribution License

16.8.2.2 Hysterectomy

Hysterectomy should be considered the treatment of choice in several indications:

- Intractable uterine bleeding
- Uterine rupture sites—multiple, longitudinal, or low lying
- Placenta percreta
- Irremediable uterine atony/accrete
- Probability of cervical cancer
- Coagulopathy?

Total Abdominal Hysterectomy

Total abdominal hysterectomy is a definitive procedure unless cardiovascular decompensation necessitates subtotal abdominal hysterectomy or simple suture repair with or without bilateral tubal ligation [257]. Previously total hysterectomy was supported because of the probability of cervical cancer in the cervical stump and increased rate of bleeding and discharge [258, 259]. The cervical malignancy rate was 0.39–1.9%. The rate has currently decreased to 0.1–0.15% due to cytological surgery [260]. It was also found that although the difference was not statistically significant, the amount of blood loss, duration of operation, and rate of maternal deaths, ABO need for blood transfusion and reoperation were higher with total hysterectomy [260]. Hysterectomy rate differs significantly in the range of 6–83% [32, 55, 79, 101, 165, 178, 179, 247, 261]. In a study with the rate of hysterectomy of

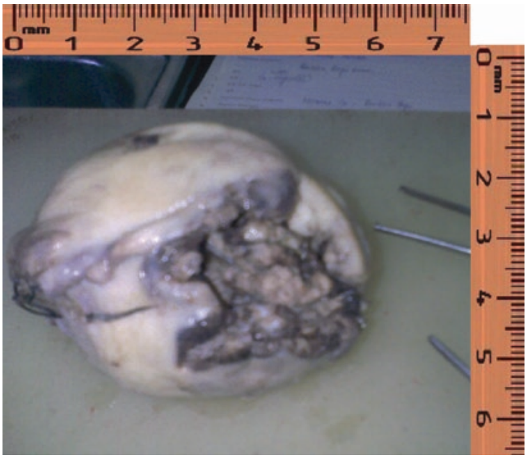

Fig. 16.25 Postoperative specimen of the uterus showing large fundal defect after spontaneous uterine rupture (unscarred uterus) due to placenta accreta. Reproduced with permission from [140]

19%, 68% were performed because the uterus was not deemed repairable, 21% for irremediable uterine atony, and 5% because of placenta accreta [79].

Placenta percreta is an additional therapeutic issue if present during spontaneous UR. Up to 1966, there were 33 cases published [262] and, in the period from 1966 to 2000, another 40 cases [263]. In cases of spontaneous UR due to placenta percreta (Fig. 16.25), partial manual removal and hysterectomy showed 20% mortality, while hysterectomy with no attempt at manual removal resulted in 100% survival. When the adherent placenta was left in situ, 67% succumbed.

> The treatment of choice for uterine rupture when placenta percreta is present is total abdominal hysterectomy with no attempt at manual removal [262, 264, 265].

When unexpected *fundal hiatus* is discovered in a presumably unscarred uterus at emergency CS for other obstetric indications, the appearance of the fibrotic edge of the defect strongly suggested a chronic event (rupture or previous perforation) with the possible expulsion of the previous conception. Hysterectomy is recommended, or if the defect is sutured, the biopsy of the edges of the defect should be sent to intraoperative or definitive histopathology [266].

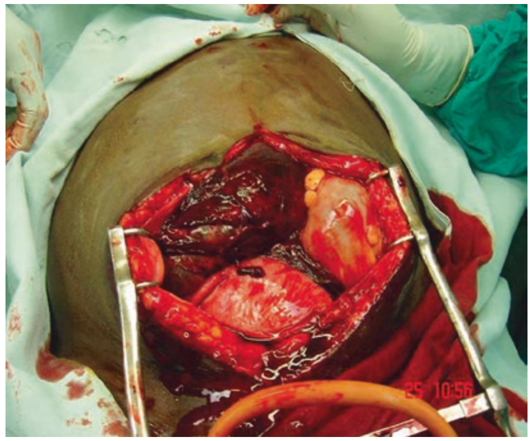

Fig. 16.26 Intraoperative photograph showing the uterus (lower part of operative field), the gestational sac (*on the left*), and the placenta (*upper right*) after opening the abdomen. Reproduced with permission from [267]

Subtotal Hysterectomy

Subtotal hysterectomy is the preferred operation when the shorter operation is indicated to minimize mortality and morbidity, as in [260]:

- Hemodynamic instability
- Cardiovascular decompensation

These recommendations are for emergency hysterectomies in general, not only spontaneous URs which represents 10% of cases [260]. In patients with spontaneous UR, total abdominal hysterectomy was done in 14%, subtotal hysterectomy in 5–22%, uterine repair with bilateral tubal ligation in 25–45%, and uterine repair without bilateral tubal ligation in 39% of patients [17, 36].

While performing subtotal hysterectomy following dehiscence of a lower-segment scar, the incision may be made posteriorly and circumferentially from the rupture [19]. In such cases, total hysterectomy carries the risk of ureteric injury. During the operation, the placenta should be examined and evacuated. It can be found in the abdominal cavity or placed intrauterine. The amniotic sac can be intact (Fig. 16.26) [226, 267] or disrupted.

16.8.2.3 First and Second Trimester

Case reports of the management of UR in the first or second trimester are limited [70–75]. Often, the clinical condition of the patients requires an emergency hysterectomy. The most important issues are whether the UR repair can withhold the tension from enlarging uterus and significant forces developed during labor. However, there have been reports with conservation of the uterus. A midgestational UR was repaired using fibrin-coated collagen fleece, allowing the successful continuation of the pregnancy [252].

16.8.2.4 Bladder Injury

Total hysterectomy may be complicated by bladder or ureteric injury [19].

> In an anterior rupture of the lower segment, the bladder should always be inspected.

The appearance of the ruptured uterus and bladder, with exposure of the trigone, is most alarming. The lower edges of the bladder tears retract posterolaterally and bleed. Friability of the edges, the proximity of the ureters, and hemorrhage all cause difficulty. The muscular cervix behind provides a firm buttress for the sutured organ. Postoperative care comprised continuous drainage of the bladder for 3 weeks and the administration of antibiotics. The instances of the above unusual and serious obstetrical injury urge us to consider carefully the anatomical relationship between the uterus and bladder and certain points in the technique of the lower-segment CS. Caudalwards to the uterovesical fold of peritoneum, the lower part of the anterior wall of the uterus and the upper portion of the vagina are in close contact with the posterior wall of the bladder. The interposition in this potential space of loose cellular tissue permits limited movement of the bladder at all times and expansion of the uterus in pregnancy. The visceral pelvic fascia is reflected upward for a short distance on to the posterior wall of the bladder and the anterior wall of the uterus and becomes fused to their connective tissue coats, on which the vesical and uterine vessels and nerves form dense plexuses. Interposed, then, between the bladder and uterus are connective tissue and blood vessels, lymphatics, and nerves.

Observation of the bladder, at different stages of filling, during abdominal operation shows that the fundal portion and the anterior wall undergo active distention, the lower posterior wall remaining relatively immobile. Apparently, free movement of the bladder on the uterus is not intended below the uterovesical fold of the peritoneum. The loose cellular tissue referred to above is composed of fine connective fibrils with abundant but poorly supported blood vessels. After surgical trauma, an organization of clot results in the formation of scar tissue, which is denser and coarser than the cellular tissue in which it develops. With infection causing edema, exudation, and fine fibrosis, scarring is still more pronounced. When, after CS, the posterior wall of the bladder becomes adherent to the transverse incision in the lower segment of the uterus, coincidental violent rupture of both organs is likely to occur if splitting or tearing should begin in the uterine scar in a subsequent pregnancy or labor.

It is obvious, then, that surgical trauma should be minimal and infection, if possible, be avoided in CS. Downward dissection of the bladder, as in total hysterectomy, is both unnecessary and inadvisable. It results in fine hemorrhages in the cellular tissue and opens the space for the spread of infection if this should occur during the puerperium. In CS the uterovesical fold of the peritoneum is picked up and divided transversely. The index finger is then inserted, and the peritoneum and underlying fascia are gently separated from the uterus immediately below the level of the incision in the peritoneum itself. This exposes the uterine muscle, into which the Cesarean incision is made. The upper limit of the bladder, with its venous plexuses, is seen, but its downward displacement, if at all affected, should be limited to the traction-force of the bladder retractor. The process variously described as "wiping-down," "blunt dissection," "gauze dissection," "disengagement," or "mobilization" of the bladder should be both gentle and slight.

The transverse incision in the uterus is sufficiently close to the cervix to be a strictly lower segment in position. In labor, the "assumption" of the cervix into the lower segment and the

expansion of that part of the uterus render a truly lower-segment section or even a laparotrachelotomy quite practicable without vigorous displacement of the bladder [19].

16.8.2.5 Elective Cesarean Section

A recurrent UR rate of 4–29% has been noted in patients with a prior repair [55, 84, 222, 268, 269], although there is one study with 18 pregnancies in which a simple repair of a ruptured gravid uterus had been previously performed with no cases of recurrent UR [270].

> A patient with previous UR can carry another pregnancy, and the women with a previous UR should undergo an elective CS as soon as fetal lung maturity can be demonstrated [156, 247, 250, 271]. CS between 37 and 38 weeks is recommended for patients with a history of the ruptured lower uterine scar, while those with a history of ruptured classical scar or previous UR, the opinion varies as to the time of delivery. Some deliver at 35 weeks, while others recommend admission to the hospital 1 week prior to the gestational age at which labor started in the previous pregnancy [84].

16.9 Prognosis

> *The fatality of this dreadful accident to the parturient female demands our sympathy, and calls for our utmost exertions to devise some means of relief, if any can be found, under circumstances presenting an almost hopeless condition of our patient; for an escape from this terrible disaster may be considered almost miraculous.*
>
> William Jackson, 1845

Maternal and perinatal mortality vary significantly between developed and developing countries. Also, these rates are highly variable in the same country especially between cities and rural areas. Due to the rarity of the disease and improvement in diagnostic and therapeutic modalities, the mortality was also decade dependent, with the continuously decreasing rate of mortality.

16.9.1 Maternal Outcome

16.9.1.1 Maternal Morbidity

The maternal morbidity rate ranges 12–46% [11, 225, 272]. Commonly reported maternal morbidity includes hemorrhage and shock, overall 46%; infection (wound infection, 13.8%; peritonitis, 10.2%; tubo-ovarian abscess or urinary tract infection, 19.8%; pelvic inflammatory disease, 4.3%; respiratory infections including pneumonia, 2.2%; and tetanus, 2%); vesicovaginal fistula, 6.6%; pelvic hematoma (mostly in the broad ligament), 19.2%; fever, 21.7%; and paralytic ileus, 18.9%.

Complications of surgery such as injury to the bladder and ureter [19], dehiscence, and hernia have been described. Less commonly, hematuria, renal failure, disseminated intravascular coagulation (DIC), atelectasis, thrombophlebitis, pulmonary and cerebral embolism, and intestinal obstruction are reported as complications of UR. In a series reported by Eden et al., 58% of patients with UR required five or more units of blood [32].

16.9.1.2 Maternal Mortality

Maternal mortality as a consequence of UR, in general, depends on several factors:

- Cause
- Decade of analysis
- Developed/undeveloped country
- Type and extension of the uterine tear
- Time of the diagnosis

Maternal mortality in the nineteenth century was 88% [168, 273], and 90% of deaths occurred within the first 10–15 min of the onset of symptoms [274]. In 1966, 29% (2/7) of patients who underwent repair of a ruptured uterus later presented with another rupture in a subsequent pregnancy, and one of these women died [222]. Maternal mortality in general occurs at a rate of 0–1% in developed countries despite rupture rates of 50% [116, 273] but in the developing countries at rate of 2–11% [17, 21, 23, 40, 257, 275, 276] and even 30% reported in Nigerian studies [38, 42, 277]. In less and least developed countries, UR is

an important cause of maternal mortality, accounting for as many as 9.3% of maternal deaths [278]. In the Second Report on Confidential Enquiries into Maternal Deaths in South Africa 1999–2001, UR caused 6.2% of deaths due to direct causes and 3.7% of all deaths (1.9% due to rupture of an unscarred uterus and 1.8% due to rupture of a scarred uterus) [279, 280]. UR was the only cause other than sepsis to have increased since the previous report, possibly due to the widespread use of misoprostol in uncontrolled dosages for labor induction [66, 281, 282]. The availability of modern medical facilities in developed nations is likely to account for this difference in maternal outcomes.

In a South African study from 1976, with the mortality rate 8.5% due to the rupture of an unscarred uterus, deaths could be further subdivided into mortality for women with longitudinal uterine tears (8.2%), transverse tears (4%), posterior wall tears (13%), and multiple uterine tears (25%). Golan et al. reported no deaths among 32 mothers who experienced a rupture of a scarred uterus compared with 15% of women with an intact uterus [55]. The maternal mortality rate associated with UR largely depends on whether the diagnosis is established before (4.5%) or after delivery (10.4%) [261]. The incidence of twin pregnancy is 5% of rudimentary horn pregnancies, and the overall survival rate is 2.4% [273]. The majority of saved patients had mean blood loss of more than 2000 mL [71, 162]. The amount of blood loss depends on the trimester of UR and on the use of uterotonics or prostaglandins for the induction of labor. These medications can decrease the amount of blood loss [108]. The mortality associated with hysterectomy was higher than for suture repair. Patients that had more extensive, multiple, or infected tears were not suitable for repair and tended to be much more acutely ill; factors contributed to the high mortality rate [38, 65].

16.9.2 Fetal Outcome

16.9.2.1 Fetal Morbidity

Significant neonatal morbidity occurs in women with UR when more than 10–37 min elapses between the onset of prolonged decelerations and successful CS [79, 101, 243]. The majority of surviving mothers had mean blood loss of more than 2000 mL [71, 162]. Maternal hemorrhagic shock is a risk factor for fetal mortality and morbidity.

Fetal Hypoxia/Anoxia/Acidosis

Leung et al. found that 5% of neonates born to women who had URs developed neonatal asphyxia (defined as umbilical-artery pH <7 with seizures and multi-organ dysfunction). No neonate had clinically significant perinatal morbidity when delivery was accomplished within 17 min of an isolated and prolonged deceleration of fetal heart rate. If severe late decelerations preceded prolonged deceleration, perinatal asphyxia was observed as soon as 10 min from the onset of the prolonged deceleration to delivery [79]. In a study by Menihan, 55% (6/11) of fetuses born after UR had bradycardias between 18 and 37 min prior to delivery. Although the rate of fetal acidosis was high (91%), no permanent neurological injuries or neonatal deaths occurred [243]. Even with rapid (<18 min) intervention between prolonged deceleration in fetal heart rate and delivery, 5–10% of neonates developed hypoxic–ischemic encephalopathies with impaired motor development [87, 118]. Although rapid intervention did not always prevent severe metabolic acidosis and serious neonatal disease, it probably did limit the occurrence of neonatal death.

In 99 cases of UR, 43% had an umbilical-artery pH <7, and 58% of these newborns had a pH <6.8. In association with these pH levels, 39% had 5-min Apgar scores of <7, and 12% of whom had 5-min Apgar scores of <3 [79]. Menihan found that 91% who were born after UR had an umbilical-artery cord pH level < 7.0, and 45% had 5-min Apgar scores <7 [243].

> The most important factor for the development of fetal acidosis is a complete extrusion of the fetus and placenta into the maternal abdomen [243].

Hypoxic–Ischemic Encephalopathy

Descriptive neonatal consequences (fetal acidosis, Apgar scores, need for resuscitation, and intensive care unit admissions) are poor predictors of neonatal morbidity. UR is associated with

a significant increase in the risk of neonatal encephalopathy, compared with a nonreassuring fetal status [283]. UR can result in an acute and profound asphyxia, and this fact might explain the predominant basal ganglia and thalamic pattern of injury observed in our newborn babies [284, 285]. One-third of delivered infants after a UR showed some grade of hypoxic–ischemic encephalopathy, and in 19% it was moderate or severe [283].

16.9.2.2 Fetal Mortality

Fetal mortality is extremely high, in the range of 54.3–81.7% [11, 21, 23, 36, 257, 275] and 91–93% in Pakistan, Uganda, and Nigeria [17, 35, 38, 39]. The perinatal mortality rate was two times lower (157/1000) in the scarred uterus group, which is significantly lower than the perinatal mortality in the unscarred uterus group (372/1000) [59]. UR was three times more likely to result in the death of the infant if the delivery took place in a hospital with <3000 births a year (1/1300) compared to hospitals with >3000 births a year (1/4700) [286]. The differences also depend on whether preterm infants are included and the kind of population studied (all women in labor vs. women undergoing a trial of labor after previous CS) [87].

Between 1990 and 2000, average gestational age and weight of newborn survivors were 32 weeks and 1770 g, respectively [273]. Fetal mortality after UR with the previous salpingectomy as a possible cause is 67% [215].

Fetal distress and neonatal demise resulting from UR are related to placental abruption and hypovolemia resulting in placental hypoperfusion, which develops rapidly. There are no comparisons of the type and the location of uterine rupture and fetal mortality and morbidity. In six cases of posterior UR after previous CS in only last case, both mother and fetus survived [29].

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17 Torsion of the Gravid Uterus

Abstract

Torsion of the gravid uterus, a frequent disorder in veterinary obstetrics, is extremely rare in humans but is more common than torsion of a nongravid uterus. Physiological dextrorotation is common in pregnancy and if additional risk factors for uterine torsion are present, such as uterine anomalies, myomas or fetal disproportions, uterine torsion has a higher incidence of occurrence. The clinical presentation of uterine torsion is variable and nonspecific. Symptoms depend on the degree of torsion, the speed at which the torsion develops, duration of torsion, and stage of pregnancy, labor or puerperium. Differential diagnosis is almost always obstetric, mostly as spontaneous uterine rupture or obstructed labor. The diagnosis should be made promptly for two reasons: (1) to save the fetus, and (2) to prevent ischemic uterine changes which could lead to uterine necrosis indicating hysterectomy. Early intervention, before irreversible uterine ischemic changes, occur enable uterus preservation with the possibility of normal future pregnancies. Detorsion is always the first operative method, and if not successful hysterotomy with Cesarean delivery helps in uterine detorsion.

17.1 Historical Perspective

No tumor, no torsion.

J. Barozzi, 1907

No uterine abnormality, no torsion.

A.L. Robinson and H.M. Duvall, 1931

The earliest report of uterine torsion (UT) in pregnancy was made by an Italian veterinarian Hippiaper Columbi in 1662 [1] because torsion of the gravid uterus is more common in animals. Almost 200 years later, in 1863, Virchow reported the first case of torsion of the nongravid uterus in a human observed at postmortem examination [2]. In 1876, this abnormality was described in a living woman for the first time by Labbe [3].

17.2 Incidence

Torsion of the gravid uterus, a frequent disorder in veterinary obstetrics, is extremely rare in humans [4–6] but is more common than torsion of a nongravid uterus. Up to 1956, there were 107 published cases in the world's literature [7]. Jensen, during the long period between 1876 and 1992, found 212 cases [8]. Between 1996 and 2006, Wilson et al. found another 38 cases [9]. A Medline search revealed only 46 cases reported since 1985 and none with a rotation ≥270° [10]. Therefore, there are less than 300 cases published in the last 150 years.

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_17

The majority is found in the third trimester [9]. The earliest reported period for UT during pregnancy is in the 6th gestational week; the latest is in the 43rd week. The majority of the torsions diagnosed at term are noted during the first stage of labor. There are only several cases in the puerperium [11–13].

17.3 Etiopathogenesis

The uterus in its normal state has little mobility and is firmly held in place by the broad ligaments and the uterosacral ligaments. These widely distributed supports resist any tendency to torsion. During pregnancy, the uterus becomes an abdominal organ with exaggerated congenital and physiological rotations and obliquities of the normal uterus. During pregnancy, there is a relatively small increase in the length of the broad ligaments causing the uterus to curve around the point of attachment. This anatomical arrangement permits an increased uterine mobility in late gestation and predisposes to the development of a UT. An additional factor is an elongated cervix with structural weakness and angulation in the isthmic region leading to torsion. The structural weakness may be developmental or acquired [14].

Physiological dextrorotation occurs commonly in pregnancy being the normal orientation of the myometrium fibers. In approximately 80% of cases, dextrorotation is present and levorotation in the other 20% [1]. A degree of rotation more than 30° is considered pathological during pregnancy, but it is not sufficient to obstruct the blood supply to the normal uterus [15]. Further rotation will give rise to symptoms depending on the degree of torsion, the stage of pregnancy, and the speed at which the torsion itself develops [16].

> Uterine torsion is defined as the rotation of the uterus on its longitudinal axis ≥45°.

In most cases, the degree of torsion is 180° [1]. Since 1985, only 46 cases in pregnancy were published and none with a rotation ≥270° [10]. However, there are cases with the rotation of 540° [17, 18] and even 720° [19] which results first in venous engorgement and then, when arterial blood supply is arrested, in uterine necrosis (Fig. 17.1) [1, 21].

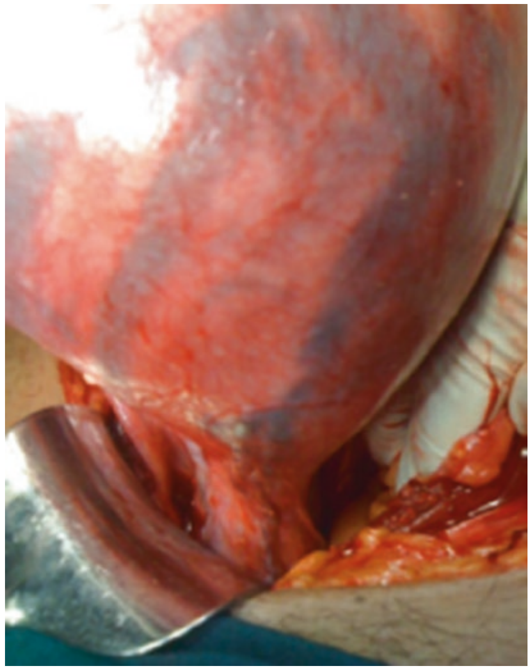

Fig. 17.1 Untwisted 180° levorotated gravid uterus with venous engorgement. Reproduced with permission from [20]

17.3.1 General Population

The presence of a uterine tumor was once believed to be the main etiological factor in the development of torsion of the uterus, and in 1907 Barozzi made the statement “no tumor, no torsion” [22]. Robinson and Duvall in 1931 modified that statement to “no uterine abnormality, no torsion,” and they presented the hypothesis that uterine rotation in the absence of gross disease was due to a developmental asymmetry of the myometrium [23]. Uterine anomalies occur in 0.1–0.5% of all women [24, 25]. The most common of these are the symmetric or duplication anomalies, including didelphic, bicornuate, and septate uteri. Bicornuate and septate uteri occur more frequently than didelphic uteri. In malformed uteri, the discrepancy in uterine vascularity and development of one-sided

muscular and fibrous attachments causes the pregnant horn to develop a high degree of mobility. Even abdominal trauma during pregnancy can be the cause [26]. For example, a large heavy fibroid of the subperitoneal type attached near the fundus of the uterus and well above the pelvic brim may rotate and exert traction on the uterus. It has inertia and a wide field of movement, and the more spherical its shape, the more easily it can rotate. When the leiomyoma is sessile, torsion of the uterus occurs at the same time as that of the leiomyoma [27].

However, in 1935, Reis and Chaloupka found 15 cases of torsion of the uterus unassociated with any uterine abnormalities, during normal pregnancy, and within a typical pelvis [10, 28]. In approximately 20% of cases of UT, no causative factor is apparent [27], although a common feature in many of these cases has been a previous Cesarean section (CS). MRI studies proved that defective isthmic healing after lower uterine segment CS may result in suboptimal restoration of normal cervical length [26, 29]. This may result in an elongated cervix with structural weakness and angulation in the isthmic region and may predispose to torsion of the uterus. Sometimes intrinsic pelvic pathology is the cause.

17.3.2 Pregnancy

The common risk factors reported in association with UT are often nonspecific and therefore not always useful in heralding this uncommon complication of pregnancy. Changes due to pregnancy play an important role, but the phenomenon is more common in nulliparous women (Fig. 17.2), while the maternal age and parity seem to play no part in causing the torsion [8, 30]. In 1931 intrinsic intrapelvic pathology is responsible for 66% of the cases during pregnancy [23], and a kyphotic pelvis is an occasional cause of torsion of the pregnant uterus [31]. According to Piot et al., 31.8% had uterine myomas, 14.9% had uterine anomalies especially bicornuate uterus, 8.4% had pelvic adhesions, 7% had ovarian cysts, 4.6% had abnormal presentation and fetal anomalies, 2.8% had

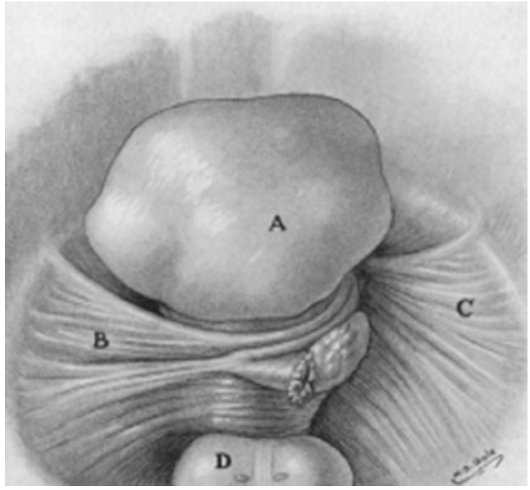

Fig. 17.2 Posterior view of the uterus. (**A**) Fibroid situated upon the fundus of the uterus; (**B**) left broad ligament (wrapped around body of the uterus); (**C**) right broad ligament; (**D**) rectum. Reproduced with permission from [27]

abnormalities of spine and pelvis, and no discoverable causes in the rest of the cases [1].

In cases of sudden fall, sudden push from other people, and bumpy movements during transportation, the fetus in the advanced pregnant uterus may respond with violent movements exposing unstable pregnant uterus to torsion. Contractions of the abdominal muscles or the degree of filling of the bladder and distention of the intestines are thought to contribute to this mechanism. Possibly excessively lax abdominal wall muscles allow UT to occur [32, 33]. Reduced amount of amniotic fluid leads to decrease in distance between a fetus and uterine wall. The fetus feels abrupt movements of the dam as a painful stimulus and, in response, performs strong reflexive movements that may cause the rotation of uterus. Reduced amount of amniotic fluid also decreases the size of the uterus that allows free intra-abdominal movement of the uterus. The twisting of the uterus makes a pressure on the middle uterine vein that results in disturbances in the venous circulation and increases the CO_2 tension in fetal blood. As a result, the fetus makes vigorous movements, and this aggravates the condition and causes the uterus to be turned more to a severe degree. This presses upon the middle uterine artery and decreases the O2 going to the fetus. If the case is

neglected, the fetus dies and may undergo emphysemation or mummification.

When previous delivery was made by CS, bladder adherence to the lower aspect of the posterior surface of the uterus (torsion of 180°) would suggest that the torsion could have taken place in the previous pregnancy just after CS [34].

The point of torsion of the uterus usually occurs at the level of the uterine isthmus [27], with three possible consequences:

1. Rotation of uterus may cause narrowing to complete obstruction of the birth canal. When this occurs, the fetus is unable to enter the cervix, and therefore the mother will not enter stage II of labor.
2. Vascular compromise which renders the uterine wall congested and fragile.
3. Delay in diagnosis results in the delivery of dead fetus since hypoxia can result from placental separation, due to venous congestion, even if the membranes have not ruptured [34].

The causative factors in pregnancy are listed in Table 17.1.

Table 17.1 Causes of torsion of the gravid uterus [7, 26, 27, 33]

Uterine myomas
Uterine anomalies, especially bicornuate uterus
Congenital weakness at the junction of cervix and uteri
Previous Cesarean section(s)
Pelvic adhesions
Abnormal pelvic architecture
Ovarian neoplasms
Abnormal fetal presentation and/or anomalies
Abnormalities of the spine or pelvis
Abdominal trauma
Sudden maternal movements
Peristaltic movements of the sigmoid colon
Bowel distention
Excessive abdominal wall muscle contraction
External cephalic version procedure
Hydramnios
Multiple gestations
Hyperactive fetus
Interstitial pregnancy
No discoverable cause

17.3.3 Puerperium

The risk factors for UT during the puerperium include fixation of the uterus by adhesions, ovarian tumor, uterine myomas, large neoplasms, and uterine Müllerian anomalies. MRI evaluation following low transverse CS suggested that, occasionally, poor healing of the hysterotomy scar may result in suboptimal restoration of normal cervical length and strength predisposing the uterus to torsion [29]. Sometimes, the association of two or more factors was described that determined the torsion—for example, uterus didelphys together with iatrogenic adhesion between one of the uteri and the pelvic wall [13].

17.4 Clinical Presentation

17.4.1 Pregnancy

17.4.1.1 Medical History

The clinical presentation of torsion is variable and nonspecific. Symptoms depend on the [16]:

- The degree of torsion
- The speed at which the torsion develops
- Duration of torsion
- Stage of pregnancy, labor, or puerperium

Therefore, the disease may be designated as asymptomatic, acute, subacute, chronic, or intermittent. The severity of the disease ranges from asymptomatic to mild abdominal pain and cramping to shock and maternal death.

In about 11% of cases, torsion is asymptomatic [7], found mostly during elective CS for other maternal [34] or fetal indications [35], mostly fetal distress [10, 36, 37]. All asymptomatic cases had UT no more than 180° [8, 35].

The gradual type is usually of 90–200° and often follows obstructed labor. The acute or fulminating type is usually with 180° or more torsion. The main clinical features are (1) pain in the lower parts of the abdomen and (2) shock

(sometimes with breathlessness, sweating [38], intestinal and urinary symptoms, obstructed labor, and secondary vaginal bleeding due to placental abruption). In cases when clinical features exacerbate progressively, patients present as "acute abdomen." Rarely does torsion of pregnant uterus occur to such an extent that the uterine circulation is arrested leading to acute maternal symptoms and also threaten fetal survival. Thus, it is usually associated with placental abruption [39]. The examination can be confounded by other obstetric diagnoses, such as abnormal fetal heart rate [2, 26, 37, 39–42] and failure to progress in labor [40, 41, 43, 44]. Urinary symptoms include urgency, frequency, nocturia, oliguria, and hematuria. Pyrexia can be a consequence of the degeneration of red fibroids that caused UT [11, 12]. UT presenting in labor [15] may manifest by the failure of cervical dilatation despite strong uterine contractions or fetal distress due to a reduction in uterine blood flow. The presenting symptoms are listed in Table 17.2.

17.4.1.2 Physical Examination

On abdominal examination, the abnormal pendulous shape of the abdomen could be found [33]. The round ligament is palpably stretched across the maternal abdomen. Uterine hypertonia can be present with uterine tenderness on palpation. On pelvic examination, the uterine artery is perceived as pulsating anteriorly. Vaginal examination may reveal vaginal bleeding, uterine tenderness, spiral twisting of the vaginal and/or cervical canal, stenosis of the vagina, uterine artery pulsating anteriorly, and urethral displacement [14]. The dorsal commissure of the vulva may be pulled forward and to left or right (twisting of the vulva).

In most cases transverse fetal lie is present [33, 37, 45, 46].

Rectal examination reveals that one side broad ligament pulled strongly downward and under the twisted uterine body and cervix and the opposite broad ligament pulled tightly across over the uterine body and cervix. Jensen described four pathognomonic clinical findings of UT [8]:

- Round ligament palpably stretching across the abdomen
- Uterine artery pulsating anteriorly on vaginal examination
- Twisting of the vagina and/or the cervical canal with the urethra displaced laterally
- Twisting of the rectum

Unsuccessful induction of labor in addition to the clinical presentation should raise the suspicion of UT. The failure of the uterus to respond to oxytocics is due to ischemia of the myometrium [47].

17.4.2 Puerperium

The clinical presentation of puerperal UT is nonspecific and may differ from the symptoms of UT during pregnancy. The most common symptom is abdominal pain varying from mild abdominal tenderness to symptoms of an acute abdomen, making diagnosis difficult. In the puerperium, a significant decrease of postpartum discharge (*lochia*), as well

Table 17.2 Presenting symptoms (in percentages) of torsion of the gravid uterus

Degree of torsion	Pain	Shock	Intestinal	Urinary	Bleeding	Obstructed labor[a]	Other symptoms	No symptoms
<90°	65	6	15	8	9	11	20	14
90°–180°	75	18	14	8	11	16	29	11
>180°–360°	100	43	50	0	7	21	21	0
>360°	100	100	0	33	17	100	0	0
Unknown	100	50	0	0	0	0	0	0

[a]Although obstructed labor was not specifically mentioned in any of the cases with torsion of more than 180°, it could nevertheless be a factor in all such cases
Reproduced with permission from [8]

as a sudden complete stop of vaginal bleeding and discharge several days after delivery, is highly suggestive of puerperal UT [13].

17.5 Differential Diagnosis

Due to the rarity of the disease and nonspecific clinical presentation with various degrees of severity, correct preoperative diagnosis is difficult. The differential diagnoses are presented in Table 17.3.

17.6 Diagnosis

Preoperative diagnosis of UT is difficult to establish. In most cases, the diagnosis is made intraoperatively. Up to 1948, there was no instance of this condition having been diagnosed preoperatively [49]. A severe torsion of the uterus can cause irreversible ischemic injury, serious thrombotic accidents, and fetal wastage. Hence, it is crucial to diagnose this condition quickly. In women who are known to have uterine anomalies which have acute severe abdominal pain in pregnancy, the possibility of UT should be considered. When fetal distress without a known cause is present, asymptomatic UT should be excluded [10, 36].

17.6.1 Plain Abdominal X-Ray

Gas in the uterine cavity—on plain abdominal radiographs and abdominal CT scan—has been described as a feature of UT in a nongravid patient and possibly can be applied to the gravid uterus also [50].

Table 17.3 Differential diagnosis of torsion of the gravid uterus [1, 4, 48]

Ectopic pregnancy
Acute hydramnios
Obstructed labor
Placental abruption
Abdominal hemorrhage
Torsion of a pelvic tumor
Peritonitis
Concealed accidental hemorrhage
Tonic uterine contraction
Degenerating fibromyomata
Uterine retroversion or incarceration
Uterine inversion

17.6.2 Abdominal Ultrasound

Ultrasound is not specific for UT in pregnancy. In some cases, if previous ultrasound scans revealed fibroids that have changed position, torsion of a myomatous uterus may be suspected [50]. Also, change of placental position [30, 46, 51] or abnormal position of ovarian and/or uterine vessels across the uterus on Doppler examination [51] may be the signs of UT. Hyperechoic area behind the placenta suggests placental abruption but not in a single case was UT suspected [43, 52, 53].

17.6.3 Abdominal CT

Gas in the uterine cavity on abdominal CT scan, as on plain abdominal radiographs, has been described as a feature of UT in a nongravid patient but probably can be applied to gravid uterus also [50]. This diagnostic imaging modality is rarely performed because the indication for exploration or CS is made mostly on the clinical ground of maternal acute abdomen or shock or fetal distress.

17.6.4 Abdominal MRI

MRI provides an accurate evaluation when the equipment and personnel are available in emergency departments. The first case of UT in pregnancy detected by MRI was by Nicholson et al. in 1995 [54]. The wall of the upper vagina changes from normal H configuration to an X-shaped configuration in UT (Figs. 17.3 and 17.4), but the plane should be at the level of the vagina on abdominal MRI [55].

17.7 Treatment

Uterine torsion in pregnancy is an absolute indication for emergent operation due to several goals:

- Prevent or stop the ischemia of the uterus.
- Prevent or stop the ischemia of the adnexa.

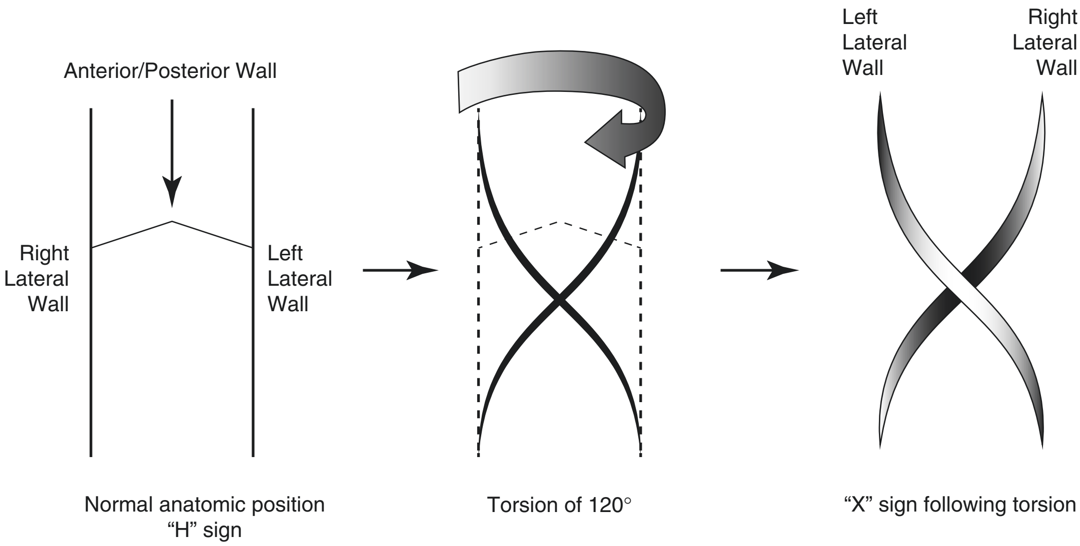

Fig. 17.3 Schematic representation of uterine torsion at the level of the upper vagina. Reproduced with permission from [54]

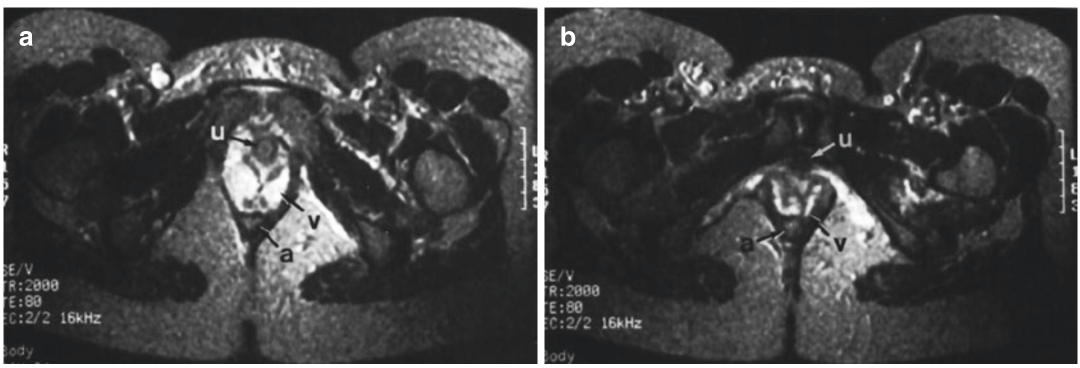

Fig. 17.4 Transverse section MRI of the vagina (*v*), urethra (*u*), and anal canal (*a*). (**a**) Distorted anatomy in uterine torsion (X-shaped configuration). (**b**) Normal anatomic position at the level of the inferior vagina (H-shaped configuration). The lower vagina is fixed at the introitus so the normal H-shaped configuration is maintained. Reproduced with permission from [54]

- Prevent placental abruption due to venous stasis and ischemia.
- Prevent or stop the hypoxia/anoxia of the fetus.

In animals there are several nonsurgical methods: (1) rotation of fetus and uterus when hands may pass through the twisted portion (for lesser degree torsion), (2) very fast rolling, and (3) rolling using plank (*Schaffer's method*).

17.7.1 Operative Treatment

17.7.1.1 Detorsion

The only therapy for a successful maternal and fetal outcome is laparotomy, CS, and correction of the torsion (Figs. 17.5 and 17.6). During exploration, the operator can observe that the anterior aspect of the uterus has an abnormal implantation of the uterine adnexa which is morphologically identical to the normal posterior aspect of the uterus implicating UT [58]. Adnexa

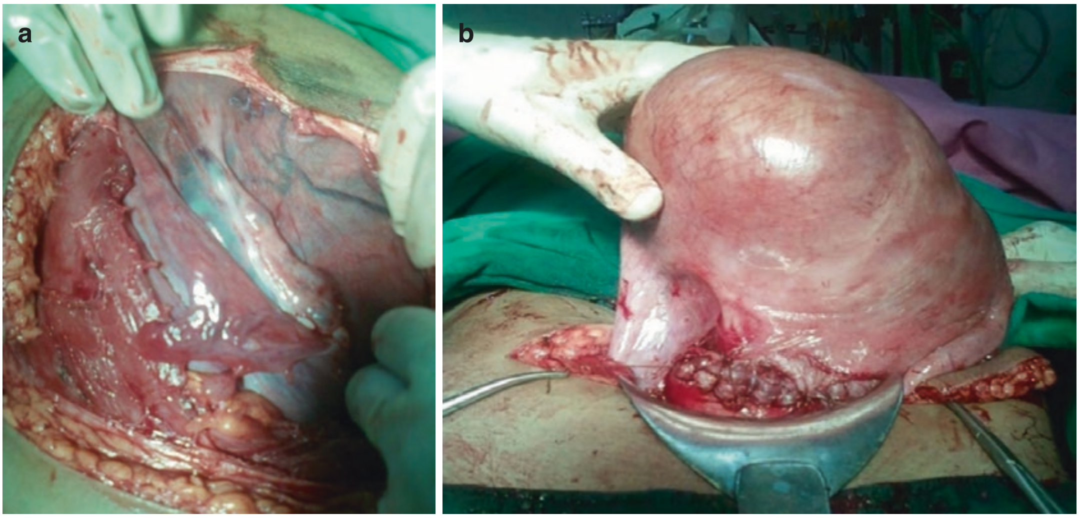

Fig. 17.5 (**a**) Posterior wall uterus with vital left adnexa turned to right; (**b**) detorsed uterus with myoma after suturing. Reproduced from [56] under the CC Attribution License

Fig. 17.6 Gangrenous ovaries due to venous stasis caused by 360° torsion of 17 weeks pregnant uterus with myoma. After detorsion ovaries became vital. Reproduced with permission from [57]

are commonly congested [59] or could be even ischemic/necrotic [59, 60]. Whether any procedure, after detorsion, or even prophylactically after CS in patients with risk factors for UT, should be performed to fix the uterus in the usual anatomic position is uncertain. Bilateral plication of the uterosacral ligaments can be done to prevent immediate postpartum recurrence of uterus torsion [52, 55]. This may help to keep the uterus in its natural position and reduce the effect of iatrogenic uterine adhesion. It may provide resistance to UT and prevent long-term recurrence [61]. The third option is bilateral plication of both the uterosacral and round ligaments [8]. In cases of UT recognized at term and manual detorsion is successful, delivery of the fetus by a CS with standard *anterior Cesarean hysterotomy* is the treatment of choice.

17.7.1.2 Hysterotomy

If detorsion is impossible, especially near the term, hysterotomy is indicated [33]. It is important to note the position of round ligaments anteriorly before hysterotomy. If torsion is not identified, the incision would be given inadvertently in the lateral wall of the uterus leading to hematoma formation. Both vertical and transverse posterior uterine incisions are indicated depending on the circumstances. The longitudinal incision in the form of a posterior classical CS is recommended when the lower segment of torted uteri is found to be inaccessible due to dense adhesions or covered with engorged venous vessels [8]. It also minimized the risk of ureteral injury. In these cases, a classical posterior hysterotomy should carry the least risk form of injury to vascular structures of the broad ligament. On the other hand, the risk of rupture, blood loss, and operating time of a *posterior transverse Cesarean hysterotomy* are theoretically less than a posterior vertical incision although the exact risk is not

known. The data on long-term consequences of posterior uterine incisions, particularly on the outcome of subsequent pregnancies, do not exist [33, 62, 63]. The anatomical landmarks should be defined before uterine incision, to prevent any inadvertent injury to blood vessels or other organs. After delivery, manual correction can be easily performed. Any predisposing factors such as adhesions, fibroids, or ovarian cyst should be removed to prevent postpartum recurrence. After deliberate posterior transverse Cesarean hysterotomy, the round ligament plication may prevent recurrent torsion in the immediate puerperium [55, 64]. Incorporating into routine practice the palpation of round ligaments at the time of CS would most likely prevent inadvertent hysterotomy at sites other than the anterior lower segment [9]. The uterine incision is closed in standard fashion with a double layer of delayed absorbable suture (polyglycolic acid suture 2-0).

17.7.1.3 Hysterectomy

- The uterus is not viable
- Women past the reproductive age
- Women do not desire more pregnancies
- Unsuccessful uterotonics during the third stage of labor

Hysterectomy is indicated when [65, 66]:
It is, however, very difficult to determine whether the ischemic injury affecting the uterus is reversible or not, especially because puerperal torsion is a rare pathologic condition [13]. In cases when low hemoglobin is encountered and the fetus is dead, bilateral uterine artery ligation should be considered before proceeding with conventional CS after untwisting the uterus to reduce intraoperative blood loss [67].

17.7.2 Obstetric Management

Obstetric decisions depend on the gestational age. Beyond 34 weeks, CS is the procedure of choice. At an earlier stage (before 23–24 weeks), the causative factor should be corrected if possible, and the pregnancy is allowed to continue to term. In the interval between the limit of fetal viability at 23–24 weeks of gestation and the 34th week or in the rare instance when imaging study accurately establishes the diagnosis before a laparotomy and signs and symptoms are not compelling, the best management is unclear. If the abdomen has been opened, and the uterus successfully rotated into the anatomic position, apparently relieving the torsion, the gynecologist must balance the unknown risk of maternal and/or fetal complications if the delivery is not accomplished against the immediate risk of substantial prematurity.

17.7.3 Anesthetic and Perioperative Management

17.7.3.1 Anesthetic and Perioperative Considerations

See Chap. 21.

17.7.3.2 Prevention and Treatment of Preterm Labor

See Chap. 23.

17.8 Prognosis

17.8.1 Maternal Outcome

17.8.1.1 Maternal Morbidity and Mortality

During the 1970s the overall maternal mortality rate associated with gravid UT was about 13%, and when UT was accompanied by malpresentation, the mortality rose to 20%. Mortality is directly related to several factors including the duration of the gestation and the degree of torsion. Under 5 months it was 0%, whereas at term it reached 18.5% [2, 8, 31]. In 1951, it was 7.4% in UT of 90°–180° and increased to 50% when the rotation was 180°–360° [8, 60]. After 1976, maternal mortality was 0% [54]. There are no reported cases of maternal death after 1960 [51]. Table 17.4 shows maternal mortality through the periods from 1876 to 1990.

Table 17.4 Maternal mortality with gravid uterine torsion by time of publication (1876–1990)

Year	Recovery (%)	Fatal (%)	Unknown (%)	Torsion > 180° (%)
1876–1899	57	29	14	0
1900–1929	83	17	0	13
1930–1959	89	11	0	16
1960–1990	98	1	1	1

Reproduced with permission from [8]

Pulmonary embolism has been described after uterine detorsion [39, 43].

17.8.1.2 Future Pregnancy

The women with UT without hysterectomy have normal fertility and can have normal future pregnancies. There are no evidence-based recommendations for women who have had a UT and who wish to have future pregnancies. The risk of uterine rupture with a prior posterior lower-segment incision compared with the risk following an anterior lower-segment incision remains unknown. In the absence of evidence, a CS is recommended for any subsequent deliveries. Theoretically, a repeated CS is safer because it avoids the possibility of a labor-associated uterine rupture [9] or repeated UTs.

17.8.2 Fetal Outcome

The limited number of cases reported and the lack of accuracy of some clinical records make fetal outcome difficult to estimate. The perinatal mortality increases with the degree of rotation, and whereas it ranges 20–24% when the uterus is rotated 90–180°, it may reach as high as 75% in cases of rotation of more than 180°. The fetal mortality rate of 18% in cases from 1996 to 2006 [9] was higher than 12% reported in the period 1876–1992 [8]. For cases before 1963, perinatal mortality was claimed to be 30.4% [45].

There are no data about fetal morbidity. Due to different compression forces and possibly impaired uterine vascularization, increased fetal morbidity is expected. There are cases of club feet deformity [63].

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Symptomatic Uterine Myoma

18

Abstract

Uterine fibroids, also known as leiomyomas or myomas, are the most common benign uterine neoplasms, especially over the age of 30. They are now observed more frequently in pregnancy because many women are delaying childbearing beyond that age. Uterine myoma can be asymptomatic or symptomatic with presentations that include red degeneration, spontaneous bleeding, obstructed labor, and torsion of the gravid uterus. It is important to accurately define the type of uterine myoma presentation. All these presentations can be defined by transabdominal or transvaginal sonography or in unequivocal cases by abdominal MRI. If bleeding is the cause, then radiologic or surgical interventions to stop the bleeding are mandatory. If red degeneration is the cause of acute abdominal pain, the therapy is conservative and symptomatic. Torsion of the gravid uterus is discussed in the separate chapter. Potential of obstructed labor is a complex issue that should be diagnosed before the labor starts to prevent emergency obstetric interventions.

18.1 Definition and Classification

18.1.1 General Population

Uterine fibroids, also known as leiomyomas or myomas, are the most common uterine neoplasms, especially over the age of 30. They are now observed more frequently in pregnancy because many women are delaying childbearing beyond that age. These are benign tumors of smooth muscle origin, with varying amounts of fibrous connective tissue [1]. Fibroids usually arise in the myometrium but may occasionally be found in the cervix, broad ligament, or ovaries [1, 2]. They are multiple in up to 84% of women [3]. Fibroids have been reported to occur in up to 70% of women by the age of 50 years [4] and are especially common in black women, who also often have more severe disease [4, 5]. Fibroids usually decrease in size after menopause. Early age at menarche and obesity are risk factors for the development of fibroids, likely due to the increased exposure to estrogen [6].

18.1.2 Classification

Uterine fibroids are classified according to their location as submucosal, intramural, or subserosal [1]. *Submucosal fibroids* are the least common type, accounting for just 5% of all fibroids [7], but they are the most likely to be symptomatic since they project into the endometrial cavity. Submucosal fibroids can occasionally become pedunculated and prolapse into the cervical canal or vagina [8]. *Intramural fibroids* are the most common type, but they are usually asymptomatic; however, they may cause infertility due to compression of the Fallopian tubes. *Subserosal*

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_18

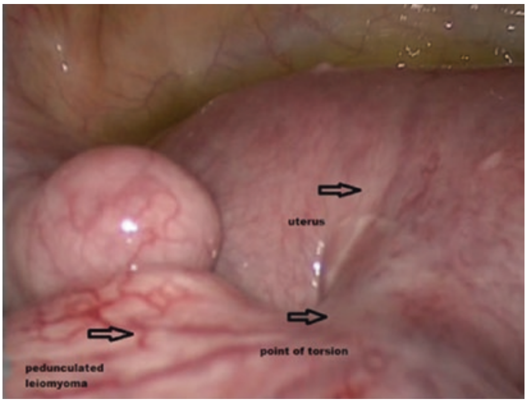

Fig. 18.1 Laparoscopic view of a huge twisted pedunculated uterine leiomyoma located at the fundus at 10 weeks of gestation. Reproduced with permission from [16]

fibroids project exophytically into the abdomen or pelvis and can also become pedunculated, which may be confused with ovarian tumors.

Pedunculated subserosal fibroids can undergo torsion (Fig. 18.1) and consequent infarction and thus be a cause of severe abdominal pain [7, 9].

Large fibroids often degenerate as they outgrow their blood supply. As the cells of the fibroid die, they are often replaced by collagen. This type of degeneration is called *hyaline degeneration*. Degeneration in fibroids may be hyaline (the most common), myxomatous, cystic, fatty, hemorrhagic, or malignant in nature [7, 10, 11]. The type of degenerative change seems to depend on the degree and rapidity of the onset of vascular insufficiency. Calcification tends to occur following necrosis [11].

Although the majority of fibroids are benign, it is thought that some uterine leiomyosarcomas arise in a subset of fibroids [12]. Only about 0.23–0.7% of apparently benign uterine fibroids turn out to be leiomyosarcomas on pathologic examination [13, 14]. Most leiomyosarcomas arise de novo. A leiomyosarcoma can be difficult to distinguish from a benign fibroid, and this possibility should always be considered in a patient with a rapidly growing uterine fibroid. Although *red degeneration* of a uterine myoma during pregnancy is managed nonoperatively, it is included in this discussion because of its ability to mimic a surgical emergency. As a myoma enlarges, it can outgrow its blood supply and undergo degeneration (muscular infarction), which occurs in up to 15% of pregnant women who have myomas [15].

Of the many complications of a uterine myoma that may occur, the spontaneous rupture of a vein coursing over its surface is rare. The complication was first reported by Karl von Rokitansky in 1861 who wrote "large or multiple fibroids exert a pressure on the uterus itself and hence an enlargement of the blood vessel which may be further stretched and occasionally be torn. In this manner, it has been noted and a tear of a subserosal vein in a fibroid led to hemorrhage into the peritoneal cavity."

18.2 Incidence

Edema and softening may result from changes during pregnancy.

Adolf Ludwig Sigismund Gusserow, 1885

18.2.1 Red Degeneration

Even before 1913, it was known that there is a relationship between red degeneration of uterine myoma and pregnancy [17]. The incidence of uterine leiomyomas varies greatly from 0.01% [18] to 1.6–2% [19] during pregnancy. In the 1920s, estimated occurrence was 0.7% [20]. Monro Kerr and Chassar Moir found the incidence to be 0.8%. In the large series from 1930 to 1954, the incidence was approximately 0.35% [21]. The explanation for the decreasing incidence of uterine fibroids during pregnancy, especially of larger sizes, is because these are removed before pregnancy or if indicated hysterectomy is made. Others claim that it is increasing because many women are delaying childbearing. These benign tumors are hormone dependent, responding to both estrogen and progesterone [22]; 15–30% of myomas increase in size during pregnancy, but most of them shrink during puerperium [23]. Red degeneration (necrobiosis) is particularly liable to occur during pregnancy. The incidence ranges 15.8–17.3%; 82% were primiparas [21]. A significant number

of patients gave a history of infertility (43%) and spontaneous abortions (25%) [18].

18.2.2 Spontaneous Bleeding

Uterine leiomyoma causing spontaneous hemoperitoneum in general female population is a very rare condition with less than 100 cases up to 1999 [24]. The first (fatal) case in pregnancy was published by Adolf Ludwig Sigismund Gusserow in 1878 (Fig. 18.2).

Precipitating factors that can cause rupture of the superficial veins traversing the surface of the fibroid include venous congestion during pregnancy, menstruation, uterine manipulation, straining at stool lifting heavy weights, and violent coitus [26].

Fig. 18.2 Adolf Ludwig Sigismund Gusserow (Berlin July 8, 1836–Berlin February 8, 1906), a German gynecologist. He began his career as a lecturer of gynecological diseases and obstetrics in Berlin and afterward was a professor at the Universities of Utrecht, Zurich, and Strasbourg. Later he returned to Berlin as a director of the Clinic of Obstetrics and Gynecology at the Berlin-Charité Hospital. Together with Christian Gerhard Leopold, he was an editor of the journal *Archives of Gynecology*. Reproduced with permission from [25]

18.2.3 Torsion of the Gravid Uterus

See Chap.17.

18.3 Clinical Presentation

18.3.1 Medical History

Although leiomyomas during pregnancy usually remain asymptomatic, they may have complications which are symptomatic. There are three principal types of nonobstetric acute abdominal presentations: red degeneration, intestinal or bladder obstruction, and intra-abdominal bleeding.

The pain of fibroid red degeneration is often sudden, severe, and localized to the site of the fibroid, usually somewhere in the pelvic area. The severe pain associated with fibroid degeneration often lasts for 2–4 weeks. In addition, unlike with torsion of an ovarian mass, there is no direct correlation between the size of the myoma and the degree of pain, but most myomas associated with abdominal pain have a volume greater than 200 cm^3 [27]. Vomiting and dehydration for red degeneration are self-limiting.

Intestinal obstruction from large myoma presents with classic symptoms of nausea, vomiting, the absence of stool and flatus, and abdominal distention [28]. The patient can present with acute urinary retention due to the obstructive pressure of myomas on the urinary bladder (see Chap. 20).

Intra-abdominal bleeding is the rarest form of presentation. Depending on the severity of bleeding only fall in hematocrit and hemoglobin can be detected taken for other symptoms [29] or the patient can present in hypovolemic shock.

Patients can present with torsion of the gravid uterus. This condition is described in detail in Chap. 17.

18.3.2 Physical Examination

Physical examination will often reveal an exquisitely tender abdomen with signs of localized

peritoneal irritation. There is tenderness over the mass attached to the uterus. Fever can be present.

18.4 Differential Diagnosis

One possible differential diagnosis of degenerating uterine myoma is uterine incarceration [30]. Incarceration is a condition in which the uterus is fixed in the hollow of the sacrum wedged between the sacral promontory and pubic rami, unable to leave the pelvis. This condition is rare and ranges 1/3000–1/10,000 pregnancies [30] and can lead to fetal growth restriction. Abdominal ultrasound or MRI can confirm the diagnosis (see Sect. 20.4.2.1). Other most common differential diagnoses are presented in Table 18.1.

Table 18.1 Most common differential diagnosis of red degeneration in pregnancy

Surgical	Gynecologic
Acute appendicitis	Hydatid mole
Acute cholecystitis	Adnexal torsion
Acute pancreatitis	Torsion of the cyst

18.5 Diagnosis

18.5.1 Abdominal Ultrasound

The ultrasound appearance of a degenerating myoma consists of a well-circumscribed uterine mass composed of echodense and echolucent areas (Fig. 18.3). Because a degenerating uterine myoma does not require surgery and has characteristic sonographic findings, it is important to consider ultrasound examination in any pregnant patient in whom emergent abdominal surgery is being contemplated. In addition to myoma size, the ultrasound evaluation of pregnant women with myomas should include position, location, relationship to the placenta, and echogenic structure. These ultrasound findings make it possible to identify women at risk for myoma-related complications and could be useful in managing the pregnancy [27].

The sonographic Doppler modality is mandatory because it helps in the decision whether to perform myomectomy during pregnancy [31].

A sharp drop in residence index in Doppler means some degree of necrosis [31].

Fig. 18.3 Ultrasound of degenerating uterine fibroid at the uterine fundus (marked with calipers). Reproduced with permission from [32]

18.5.2 Abdominal MRI

Magnetic resonance imaging (MRI) can be safely used during pregnancy to evaluate uterine or adnexal masses (Fig. 18.4), but a small percentage of cases was evaluated by MRI previously [33, 34]. MRI also confirms the status of the fetus, its relation to uterine myoma(s), and relation of uterine myoma(s) to other intra-abdominal structures (Fig. 18.5). Intra-abdominal bleeding possibly caused by bleeding myoma can also be found (Fig. 18.6).

18.6 Treatment

> *Operative management is contraindicated, for the symptoms subside with rest in bed, and further complications such as infection, are mostly unknown.*
>
> Wilfred Shaw

18.6.1 Historical Perspective

In 1920, William Mayo reported 19 myomectomies during pregnancy. Five of the patients

Fig. 18.5 Abdominal MRI without contrast shows a 10-week gravid uterus with pregnancy in the fundus (*star*), compression of the colon (*empty arrow*), and compression of the urethra (*filled arrow*). Reproduced from [35] under the CC BY 2.0

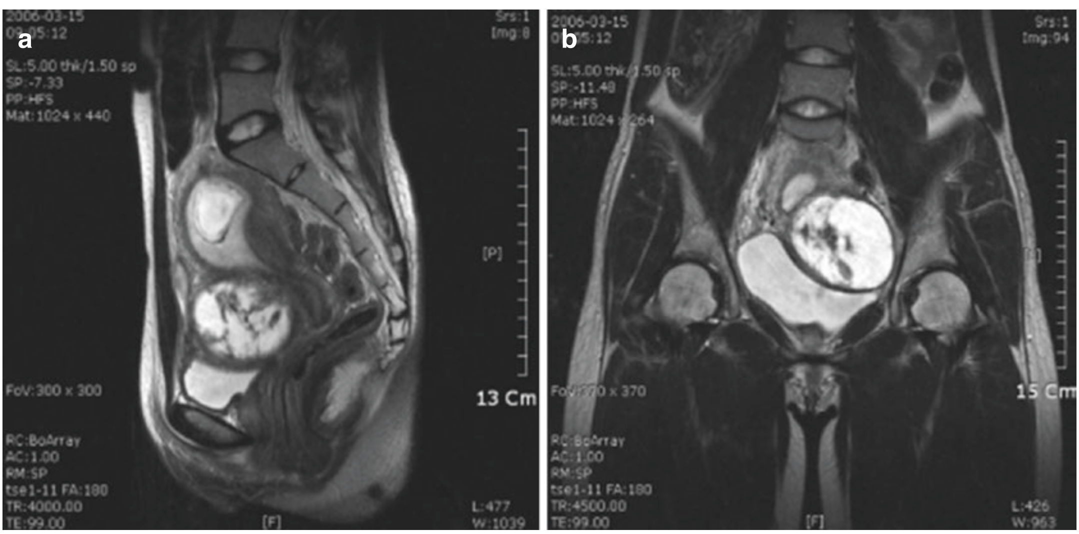

Fig. 18.4 T2-weighted image of MRI findings of a 12-week pregnant woman shows an 8 × 7 × 6 cm cystic and solid mass with septa. (**a**) Sagittal view; (**b**) coronal view. Reproduced from [33] under the CC BY 3.0

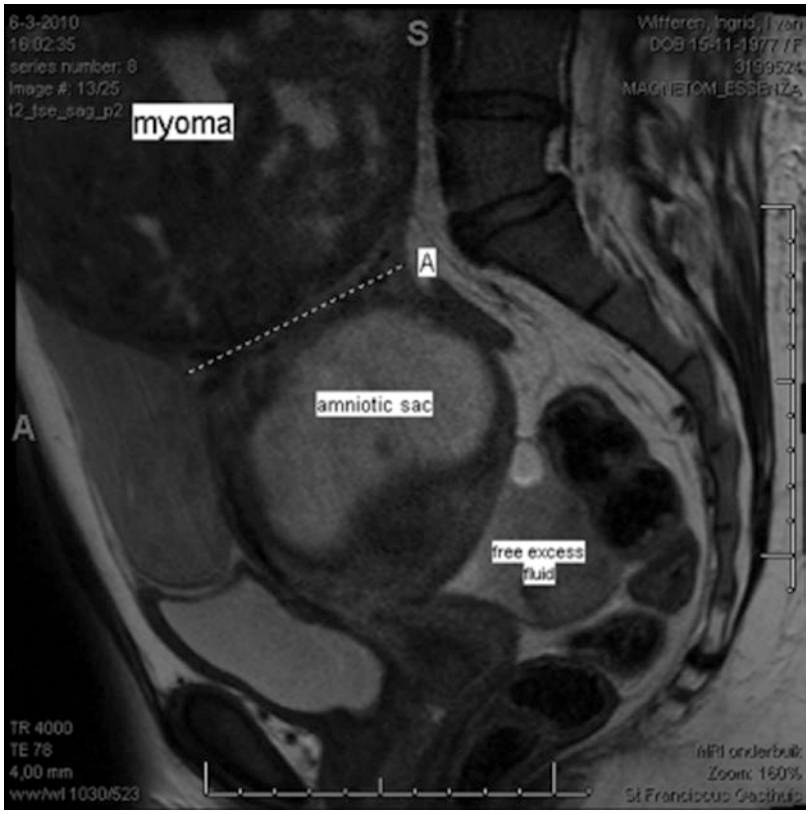

Fig. 18.6 Fluid in the pouch of Douglas seen on abdominal MRI, indicating intra-abdominal bleeding. Large subserosal myoma is seen above the gestational sac. Reproduced with permission from [29]

showed signs of impending miscarriage prior to operation, and in three the miscarriage was averted by the operation [36].

18.6.2 Emergent Presentation

The relationship between myoma volume and myoma growth in the different gestational periods was not statistically significant. On the other hand, when myoma volume was related to complications during pregnancy or at delivery, a statistically significant difference was observed. Myomas with volumes >200 cm^3 show a higher rate of complications than those with volumes ≤100 cm^3 [37].

Despite an often dramatic presentation, the optimal treatment for a degenerating uterine myoma is a short course of analgesics. Pain will often improve dramatically soon after treatment is initiated. The local release of prostaglandins from a degenerating fibroid can also stimulate uterine contractions and premature labor, so prompt consultation with an obstetrician/gynecologist is strongly advised when this complication is identified. Myomectomy is inevitable in about 2% of cases [38].

Sometimes genuine doubt with a right-sided fibroid low in the iliac fossa mimicking appendicitis forces the surgeon to do an exploration. The severity of symptoms and suspicion of malignant mass or torsion are key in deciding upon the indication for emergent operation.

Kim and Lee recommend cyst aspiration rather than myomectomy in a myoma with cyst degeneration and pain [33]. Occasionally a well-pedunculated fibroid may be easy to remove, but no attempt should be made to dissect out sessile or buried tumors. Once the real condition is apparent, usually the abdomen should be closed with no attempt at myomectomy, a particularly bloody operation at this stage of pregnancy. There has been only one successful case of a gasless laparoscopic myomectomy [39]. In this

case, it was difficult to differentiate a complex ovarian mass from cystic degeneration of the myoma.

It is important to emphasize that augmented vascularization and tissue impedance of the pregnant uterus can amplify the risk of electrosurgical damage. It is therefore important to avoid the use of monopolar and bipolar electrosurgery in the myoma resection [40]. Electrocautery and an argon beam coagulator to minimize blood loss have been described, with good results [41]. After excision or extirpation, the defect should be closed with sutures and adequate hemostasis obtained.

Preoperative diagnosis of bleeding uterine myoma is rare [42, 43]. When bleeding subserosal myoma is found (Fig. 18.7), the uterine serosa is opened in order to identify the capsule of the myoma before dissection of the peduncle. Then the clamps are placed on the peduncle and the myometrium sutured with 1–0 resorptive sutures.

Another indication for emergent management is acute urinary retention due to: (1) direct compression of urinary bladder by uterine myoma or (2) uterine myoma causing uterine retroversion with resultant acute urinary retention (see Sect. 20.4).

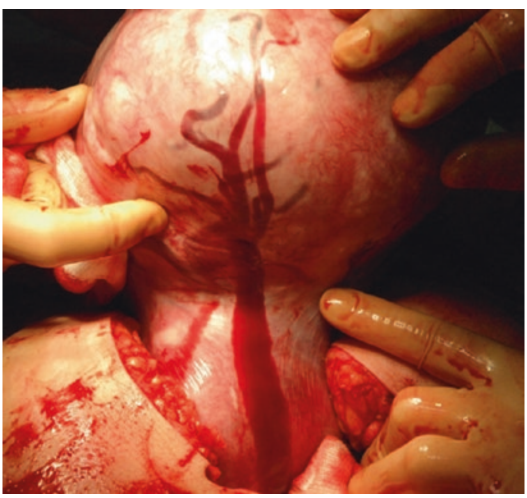

Fig. 18.7 A 10-week gravid uterus with pedunculated myoma. Large ruptured vein causing massive intra-abdominal bleeding. Reproduced with permission from [29]

18.6.3 Elective Presentation

Elective treatment depends upon the: (1) location of the uterine fibroid, (2) size and a number of the uterine fibroid(s), (3) relation to the placenta, and (4) gestational age. Four options are available:

- Hysterectomy
- Abortion with the removal of the tumor subsequently
- Myomectomy with or without removing the fetus
- The progress of pregnancy and solving emergencies if they arise

18.6.3.1 Myomectomy

Cesarean Myomectomy

Cesarean myomectomy (myomectomy at the time of Cesarean section—CS) can be hazardous because of uncontrollable hemorrhage. Most obstetricians advise against myomectomy at the time of CS [27], unless the myoma is pedunculated [18, 44]. Others even advocate elective myomectomy in order to minimize postoperative sepsis and postpartum hemorrhage [41]. Most obstetricians would agree that myomectomy at the time of CS (Fig. 18.8) should be carried out on only carefully selected women and only by senior obstetricians [44]. Although intramural fibroids can be safely removed during CS, large fibroids and extra incisions for myomectomy are risk factors for hemorrhage [45].

Myomectomy

Twisted pedunculated uterine leiomyoma is untwisted first. Subsequently, a linear cutting stapler is fired across the stalk of the pedunculated leiomyoma at the point of torsion. Some perform (incidental) appendectomy [16]. The specimen(s) are removed using a nylon extraction bag introduced through the left lateral trocar site and the incision extended (if needed) to enable removal of the bag with its contents. The laparoscope is reinserted, the staple line is assessed for hemostasis (Fig. 18.9), and peritoneal irrigation is carried out.

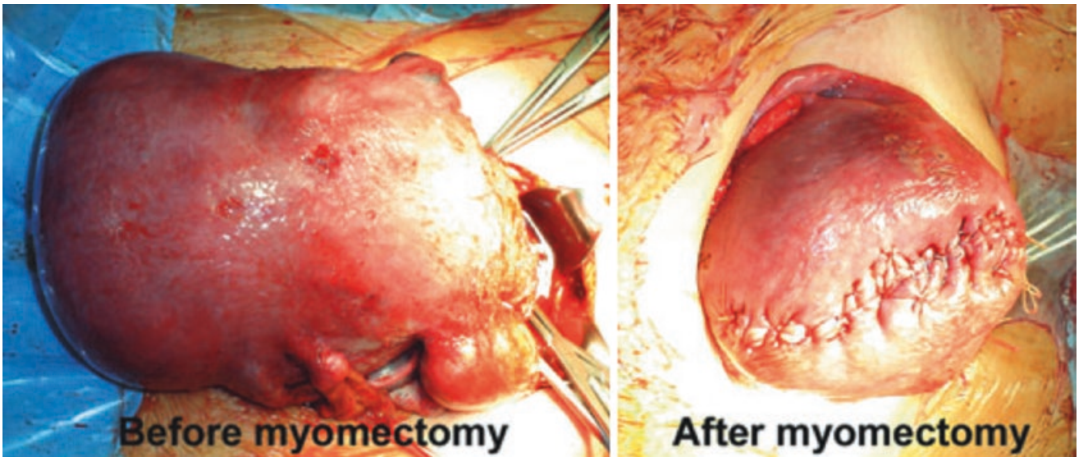

Fig. 18.8 Before and after myomectomy during Cesarean section. Reproduced with permission from [46]

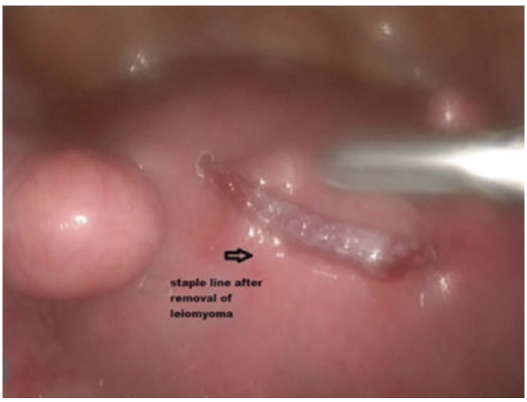

Fig. 18.9 Staple line after myomectomy at 10 weeks of pregnancy, assessed for hemostasis. Reproduced with permission from [16]

After any-cause myomectomy in pregnancy, CS is the mode of delivery in 94% of the cases [47].

18.6.4 Perioperative Management

18.6.4.1 Anesthetic and Perioperative Considerations

See Chap. 21.

18.6.4.2 Prevention and Treatment of Preterm Labor

See Chap. 23.

18.7 Prognosis

18.7.1 Maternal Outcome

18.7.1.1 Maternal Mortality

The type of presentation dictates the maternal outcome. When red degeneration is present, maternal mortality is 0%. When spontaneous uterine fibroid bleeding is the cause, then there is a potential for maternal death. Up to 1903 maternal mortality was 75%, and during the 50 years (1921–1972), it rapidly declined to 0% [42] and remained the same until today [29, 43, 48].

18.7.1.2 Maternal Morbidity

In a prospective study of 13 myomectomy cases during pregnancy, there was no blood transfusion and other complications [49].

18.7.2 Neonatal Outcome

In 71 cases, only two pregnancies were terminated after myomectomy [50, 51], and two cases had preterm labor and preterm delivery, respectively [49, 52]. One case had intrauterine growth retardation [50]. In one large prospective study, in 13 cases myomectomy was done, and there were 12 cases of live births [49]. These series

show excellent neonatal survival in the range of 92–97%. The rate of pregnancy loss seems similar both in patients treated surgically and in patients treated expectantly [27, 47, 52, 53].

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19 Complicated Pelvic Inflammatory Disease

Abstract

Pelvic inflammatory disease is rare during pregnancy. The most obvious reason is that many pregnancies are more or less desired, and one of the preparations is prepregnancy treatment of any disease, especially of reproductive organs. Pregnancy is said to protect against pelvic infections, and clinicians are therefore unlikely to suspect complicated pelvic inflammatory disease as a cause of an acute abdomen in pregnancy. Modern factor that adds to the incidence of pelvic inflammatory disease during pregnancy is assisted reproductive technology with inoculation of infective pathogens to the peritoneal cavity. Therefore, techniques for prevention of infection inoculation during assisted reproductive technologies are mandatory and discussed in detail. Clinical presentation is the same as in nonpregnant population with the same differential diagnoses. Before the widespread use of abdominal sonography, preoperative or prelabor diagnosis was rare. Today, modern imaging techniques such as abdominal CT or MRI accurately define the type and severity of the pelvic inflammatory disease. This is important due to different therapeutic modalities available.

19.1 General Female Population

For easier understanding of the pelvic inflammatory disease (PID) characteristics in pregnancy, some considerations, in the female population, are presented. Not all causes and not all clinical manifestations are presented, only complicated PID that mostly manifests as acute abdomen during pregnancy.

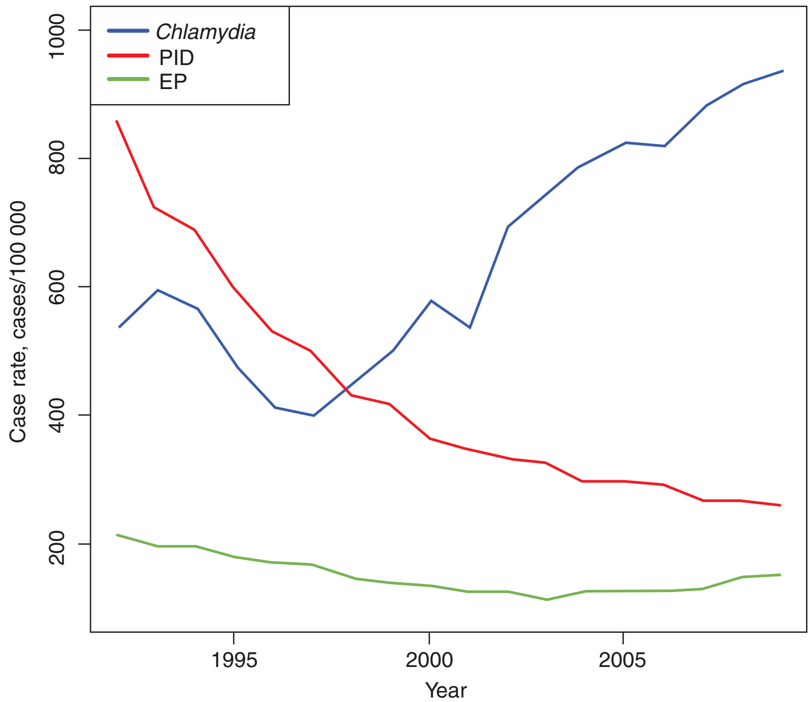
19.1.1 Tubo-Ovarian Abscess

19.1.1.1 Incidence

Despite an increase in the number of effective broad-spectrum antibiotics, PID and the complications arising from the disease continue to reach epidemic proportions into the 1990s. Acute salpingitis and PID account for more than 350,000 hospital admissions and 150,000 surgical procedures per year [1]. Also, nearly one-third of patients hospitalized for PID develop some degree of pelvic abscess [2]. Other sequels such as ectopic pregnancy, salpingitis isthmica nodosa, tubal infertility, chronic pelvic pain syndromes, and pelvic adhesions are other consequences of PID (Fig. 19.1).

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_19

Fig. 19.1 Case rates for *Chlamydia trachomatis* infection (age, 15–39 years), pelvic inflammatory disease (age, 15–44 years), and ectopic pregnancy (age, 15–44 years), British Columbia, Canada, 1992–2009. *PID* pelvic inflammatory disease, *EP* ectopic pregnancy. Reproduced with permission from [3]



19.1.1.2 Pathophysiology

Tubo-ovarian abscess (TOA) is the most serious manifestation of salpingitis because the intra-abdominal rupture of a TOA is potentially life-threatening, with mortality rates as high as 8.6% [4]. PID and subsequent TOA may result whenever bacteria gain access to the upper female genital tract. Under normal circumstances, the Fallopian tubes and related pelvic structures are sterile. However, access of bacteria to the upper genital tract either via sexually transmitted diseases or through instrumentation of the uterus may inoculate the uterus with bacteria from the vagina, causing infection. It has been suggested that passive transport and vectors such as spermatozoa and *Trichomonas* assist in establishing the ascending infection from the polymicrobial vagina and cervix [5]. Once present in the upper genital tract in sufficient numbers and virulence, these bacteria initiate an inflammatory reaction (endometritis-salpingitis-peritonitis) that results in the signs and symptoms of PID. The rate of a TOA developing from typical PID is in the range of 1–4% [6].

19.1.1.3 Microbiology

TOA is usually a polymicrobial infection, whereas general pelvic infections may often be monomicrobial. TOAs are usually a mixture of anaerobic, facultative anaerobic, and aerobic organisms, with the purest isolated being anaerobes. The most frequent isolates from TOAs include a variety of *Enterobacteriaceae*, such as *E. coli* (37%), *B. fragilis* (22%), and other *Bacteroides* spp. (26%), *Peptostreptococcus* spp. (18%), and *Peptococcus* spp. (11%) [4, 7]. The sexually transmitted organisms such as *N. gonorrhoeae* and *C. trachomatis* are usually not present in the abscess but may be recovered from the cervix in one-third of cases. The emergence and recognition of *Prevotella bivia* (formerly *Bacteroides bivius*) and *Prevotella disiens* as major pathogens in upper female genital tract infection, combined with data suggesting that increased concentration of anaerobic organisms in the vagina is a risk factor for PID, point toward an anaerobic-predominant mixed infection as a cause of PID and TOA. These anaerobic bacteria such as *Bacteroides* spp. and *Peptostreptococcus* spp. are commonly found in

high concentrations in the vagina of women with bacterial vaginosis [5].

19.1.1.4 Clinical Presentation

The clinical diagnosis of TOA has the same diagnostic difficulties of PID. Women presenting with PID and a pelvic mass may have a TOA, or it could be a hydrosalpinx, tubo-ovarian complex, or other complex adnexal mass. Patients with TOAs typically present with a history of pelvic or abdominal pain and fever. A history of PID may be present in only 50% of patients. A significant proportion of women with TOA are afebrile (20–30%) (and these have normal WBC counts) [2].

Pelvic examination usually reveals extreme pelvic tenderness (cervical motion tenderness), and mass may be present. If rupture has occurred, typical signs and symptoms of peritonitis are present and may lead to septic shock.

19.1.1.5 Diagnosis

The majority of patients have a leukocytosis, but afebrile patients can have normal WBC levels [2]. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may help in the diagnosis. CRP was found to be more sensitive than elevated WBC or ESR.

Ultrasonography is very reliable in the diagnosis of TOAs and in following TOAs that are managed conservatively [7]. The expected typical appearance of a TOA on ultrasonography is a complex or cystic adnexal mass with multiple internal echoes and septations. The "gold standard" for diagnosis has always been laparoscopy; however, as ultrasound technology continues to improve, laparoscopy may be reserved for patients in whom the diagnosis is questionable.

Criteria for PID in general female population can apply to pregnant population (Table 19.1).

Table 19.1 Major and additive criteria for the diagnosis of PID

Major criteria
The absence of these criteria tends to rule out a PID diagnosis:
• spontaneous pelvic pain (in the absence of another disorder)
• induced adnexal pain
• pain on uterine mobilization
Additive criteria
Each of these criteria increases the probability of PID:
• history: Sexually transmitted infection; postpartum or postabortion; recent endouterine maneuvers; rectal syndrome (tenesmus, other anal spasms); vaginal bleeding
• clinical examination: temperature >38 °C; purulent leukorrhea
• laboratory tests: Elevated C-reactive protein; presence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Mycoplasma genitalium* on bacteriological examination; endometritis on endometrial biopsy sample; salpingitis on fimbrial biopsy sample
• ultrasonography: Thickening of the tubal wall (>5 mm); cogwheel sign (thickened tubal fringes resembling incomplete septa); heterogeneous latero-uterine mass potentially septated with fine echoes

PID pelvic inflammatory disease
Reproduced with permission from [8]

19.1.1.6 Treatment

Indications for surgical intervention in the treatment of TOA are same in nonpregnant and pregnant population (see Sect. 19.9).

Intraperitoneal rupture of a TOA represents a true surgical emergency, but the extent of the surgery required to achieve a cure is controversial [7, 9]. Traditionally, aggressive surgical extirpation, usually consisting of the total abdominal hysterectomy with bilateral salpingo-oophorectomy and drainage of all pockets of infection, was the treatment of choice. This radical approach was used largely because of the inadequacies of antibiotics of that time. This procedure dropped the mortality rate from 100% to 12% [10] and could be the procedure of choice in a patient who has completed childbearing. In patients with the severe complicated disease, total abdominal hysterectomy with bilateral adnexectomy may be necessary despite the patient's reproductive status. Patients without adnexa are still able to conceive via in vitro fertilization and embryo transfer (IVF-ET). Subtotal hysterectomy can also be successfully performed [11]. Antibiotic therapy should include a broad-spectrum cephalosporin such as cefoxitin or cefotetan. Anaerobic coverage with clindamycin or metronidazole is mandatory, as these have been shown to have the best ability to penetrate an abscess [7].

However, most women who present with a TOA are at the peak of their reproductive years, and fertility is a major issue. Conservative surgery should be attempted if the pathology is limited to only one side of the adnexa, and further reproduction is desired [12]. Conservative therapy of PID (Table 19.2) or an unruptured TOA (Table 19.3) consists of appropriate intravenous antibiotic therapy [13], close monitoring of the patient, and possible drainage of the abscess via posterior colpotomy [13–15], CT- or ultrasound-guided percutaneous drainage, or drainage via laparoscopy. The posterior colpotomy approach has largely been abandoned because of a high rate of complications. Success rates of CT-guided percutaneous drainage are in the range of 77–94% [16]. Early drainage of abscess and irrigation via laparoscopy in addition to antibiotics achieved a success rate of 95% [17]. Drainage of a TOA in combination with antibiotic therapy is much more successful than conservative management. Patients treated with antibiotics alone have 50–70% success rate. Remaining patients eventually require surgical treatment for the disease [2, 5, 18]. Approximately 19% of patients treated with conservative surgical therapy require reoperation at a later date [2, 18, 19]. In cases of the grossly apparent bilateral disease, a somewhat conservative approach of bilateral partial adnexectomy without hysterectomy may be performed.

Table 19.3 Proposed antibiotic therapies for the treatment of tubo-ovarian abscess in general population[a]

Substance[b]	Dosage	Route	Duration, d
First-line treatment			
Ceftriaxone	1–2 g once a day	Intravenous	14–21
Metronidazole[c]	500 mg three times a day	Intravenous	
+ doxycycline[c]	100 mg twice a day	Intravenous	
Alternatives[d]			
Ofloxacin[c]	400 mg twice a day	Intravenous	14–21
+ metronidazole[c]	500 mg three times a day	Intravenous	
Cefoxitin	1–2 g three times a day	Intravenous	14–21
+ doxycycline[c]	100 mg twice a day	Intravenous	

[a]In cases of septic shock, severe sepsis, or immunodepression, 3–8 mg/kg/d gentamicin can be added in a daily intravenous injection, for no more than 5 days
[b]Reassessment of the antibiotic therapy at 72 h on the basis of the clinical and microbiological results is essential. In the case of a de-escalation of the antibiotic spectrum, it is recommended that treatment against anaerobic microbes and *C. trachomatis* continue until the therapy is completed
[c]Because oral bioavailability is good for ofloxacin, metronidazole, and doxycycline, it is possible to administer them orally as soon as the patient is no longer running a fever, has no gastrointestinal disorders, and has shown some clinical improvement
[d]These protocols do not cover all bacteriological situations (e.g., resistance of some gonococcal species to fluoroquinolones, the resistance of some enterobacteria species)
Reproduced with permission from [8]

Table 19.2 Protocols for antibiotic therapy of uncomplicated PID in general population

Antibiotics	Dose and route	Duration	Comments
First-line treatment			
Ofloxacin	400 mg twice a day, oral	14 days	
Metronidazole	500 mg twice a day, oral	14 days	–
Ceftriaxone[a]	500 mg im. Injection	–	–
Possible alternatives			
Ceftriaxone[b]	500 mg im. Injection	–	–
Azithromycin[b]	1 g per week	14 days	Limited efficacy against anaerobes
Moxifloxacin	400 mg/day	14 days	Higher cost; precautions for hepatic disorders
Ceftriaxone[c]	500 mg im. Injection	–	–
Metronidazole[c]	500 mg twice a day, oral	14 days	–
Doxycycline[c]	100 mg twice a day, oral	14 days	–

[a]Can be used if necessary
[b]Used together
[c]Used together
Reproduced with permission from [8]

19.1.2 Ovarian Abscess

19.1.2.1 Historical Perspective

Black presented the first major series of 105 cases in 1936 [20]. The incidence of OA in all cases of PID was 6%, while others cited in that study claimed incidence 12.4–15.45%. Wetchler and Dunn have reported 120 cases in the female population in literature till 1985 [21], and Stubblefield in 1991 added 5 cases [22].

19.1.2.2 Pathophysiology

OA is a primary infection of the parenchyma of the ovary, an entity distinctly different from TOA. TOA, by contrast, involves the ovary by secondary spread from the infected Fallopian tube [21]. Ascending infection is the most important mode of infection in nonpregnant women. OA has also been reported due to non-gynecologic conditions such as ruptured acute appendicitis or colonic diverticulitis or secondary to infection at distant sites as in tonsillitis, typhoid, parotitis, and tuberculosis. Association of OA with an intrauterine device (IUD) has been noted, and some of them may be secondary to *Actinomyces* spp. It may also occur due to secondary infection in a dermoid cyst, serous cystadenoma, or simple ovarian cyst.

19.2 Incidence

19.2.1 Acute Salpingitis

Acute salpingitis in pregnancy is exceptionally rare. Up to 1959, there were six cases published [23, 24]. Most cases presented during first 8 weeks of pregnancy at that time [23].

19.2.2 Tubo-Ovarian Abscess

In the 6th edition of *Antenatal and Postnatal Care* by Francis J. Browne from 1946 [25], it is stated that salpingitis does not occur during pregnancy. Even at that era and decades before this 6th edition, there were published cases of PID during pregnancy [26–36]. First published cases were by Auguste (Marie Joseph Victor) Brindeau (Fig. 19.2) in 1917 [37]. In addition to 12 personal cases of salpingo-oophoritis during pregnancy, Brindeau has collected 81 more cases, of these 44 were operated on [31]. Today it is known that PID, in the form of pelvic and peritoneal abscess, complicates pregnancy, but it is rare due to several reasons. First, in cases of wanted pregnancy, future mothers live healthy life avoiding any risks, including sexually transmitted diseases. In addition, especially women that had "gynecological problems" visit their gynecologists more often to eliminate any possibility that can interfere with future normal pregnancy. Diseases found in that prepregnancy period are cured, minimizing the possibility of disease flare during pregnancy.

Acute salpingo-oophoritis or pelvic abscess during pregnancy occurs more commonly in the first trimester [38, 39] and almost always found on the right side [40, 41]. There is no predilection in IVF-ET because TOA starts on the side of oocyte retrieval (Table 19.4). By 1977, only 12 cases of TOA occurring late in pregnancy had been published [37] and up to 2014, only 34 cases [42–45]. There are several newer cases afterward [46]. On the other hand, pelvic infection readily occurs in the puerperium if there is an infection of the birth canal during or following parturition. Pelvic infection after transvaginal oocyte retrieval for IVF-ET is <1% [47–50]. In less than half of these cases, a pelvic abscess develops [48]. All collected cases of TOA after IVF-ET pregnancies are presented in Table 19.4.

19.2.3 Ovarian Abscess

Aitken made the earliest description of primary (ruptured) ovarian abscess (OA) in pregnancy in 1870 [60]; then three patients were described by Coe in 1891 [61]. Öhman in 1913 operated 7 days after a normal delivery upon a woman, who presented acute pelvic symptoms with a mass to one side, which proved to be a streptococcic pyoovarium [36]. Tenani, in 1921, reported the

Fig. 19.2 Auguste (Marie Joseph Victor) Brindeau, a French gynecologist (1867–1955) who worked in Paris, finally at the *Clinique Tarnier* where he retired. He was one of the founding members of the journal *Gynécologie et Obstétrique* in 1919 (reproduced from [51]; webpage Biusanté Paris)

rupture of a pyo-ovarium during the second stage of labor [62]. Although the true incidence of OA is unknown, it seems that it is extremely rare in pregnancy [21, 36, 60–64, 45, 65–72, 56].

19.2.4 Intramyometrial and Uterine Horn Abscess

These entities are not described as part of PID, but it is mentioned here due to the same possible etiological factors. These are the rarest entities with only one report for both intramyometrial (two cases) [73] and uterine horn abscess [74] found.

19.3 Etiopathogenesis

Sometimes a pus tube forms after conception has occurred, the woman having been infected and impregnated at the same time.

Joseph Bolivar DeLee, 1938

19.3.1 Suppurative Salpingitis

19.3.1.1 Acute Suppurative Puerperal Salpingitis

Detailed pathophysiology and progression of acute puerperal salpingitis were described by Aleck W. Bourne in 1921 [75]. Acute puerperal salpingitis differs in many aspects from that of nonpuerperal origin. Essentially, the Fallopian tubes are abdominal and not pelvic organs, and they are usually affected before they have reached their normal positions in the pelvic cavity.

By the end of the first week when symptoms are generally manifested, the Fallopian tubes lie at, or just above the pelvic brim, in relation to the iliac vessels, while the ovaries are placed below, just within the pelvis, and applied to its lateral walls. The former is, therefore, outside the limitation of the pelvic basin and is surrounded by coils of the small intestine; this considerably alters the results which will follow the escape of pus from the abdominal ostia, as com-

Table 19.4 Clinical features of tubo-ovarian abscess in pregnancy after IVF-ET (reproduced from [44] under the CC Attribution License)

Case	Vaginal preparation method[a]	Interval from IVF to symptom (wk)	History of endometriosis	Time of OP[b] (wk)	WBC[c]	Pain	BT (°C)	Mass (cm)	Procedure	Pregnancy outcome
Padilla [52]	Betadine	3	+	GA 5	12,400	+	38.5	CDS, 5	Laparoscopic drainage	Ongoing singleton IUP, GA 7 weeks
Zweemer et al. [53]	NA	42[d]	NA	GA 38[d]	18,700	+	38.6	Right, 16	Laparotomic removal	Healthy singleton baby 3240 g under CS at GA 38 weeks
Younis et al. [54]	IV antibiotics	3	+	Not done	21,000	+	38.9	Bilateral, 6	Antibiotic treatment	Healthy singleton baby 2850 g at full term
Den boon et al. [55]	NA	23	+	GA 25	17,700	+	38.0	NA	First drainage, second diagnostic laparotomy	c 1/3—Expire at 9 weeks
Matsunaga et al. [42]	NA	14	+	GA 22[e]	Raised	+	38.1	Left, 8	Laparotomy–LSO	Vaginal delivery at GA 22 weeks, Apgar 1/3 –expired
Jahan and Powell [56]	NA	3	+	GA 6	Raised	+	39.0	Left, 7.8	Laparoscopic drainage (two times)	Elective CS at GA 37 weeks (fetal cardiac anomaly)
Sharpe et al. [57]	Saline, PO antibiotics	11[f]	+	GA 31	30,600	–	–	Right, 10	CS and drainage	Healthy twins, GA 31 weeks
Al-Kuran et al. [58]	Saline	7	–	GA 9, GA 21[g]	15,000	+	+	Left, 5	Laparotomy–appendectomy drainage (two times)	Spontaneous abortion at GA 21 weeks
Park et al. [44]	Saline, PO antibiotics	12	+	GA 14	10,330	+	–	Right, 12.5	Laparoscopic drainage	Ongoing singleton IUP GA 25 weeks
Pabuccu et al. [45]	PO antibiotics	3	–	GA 3	12,500	+	38.3	Left, 4.5	Laparoscopic drainage	Twins dead at GA 8 weeks
Biringer et al. [59]	No antibiotics	16	–	17	36,000	+	37.8	Right, 15 mL	Laparotomic drainage	First fetus – At GA 16 weeks – Expired, spontaneous abortion Second fetus – Vaginal delivery at GA 30 weeks (1330 g, Apgar 7/8/8 -live

IVF in vitro fertilization, *ET* embryo transfer, *OP* operation, *WBC* white blood cell count (/mm3), *BT* body temperature, *GA* gestational age, *CDS* cul-de-sac, *IUP* intrauterine pregnancy, *NA* not available, *IV* intravenous, *LSO* left salpingo-oophorectomy, *PO* per oral, *CS* Cesarean section.

[a]It contains vaginal irrigation method in oocyte retrieval and use of peri-retrieval antibiotics.
[b]The time of the first operation for a tubo-ovarian abscess.
[c]All data are at the time of diagnosis.
[d]Symptom was developed 45 days after CS at 38 weeks.
[e]Operation was done 15 days after delivery at 22 weeks.
[f]She had only painless vaginal discharge at the first time.
[g]The second operation was done 24 h after delivery at 21 weeks.

pared with a similar tubal condition in which the tubes are lodged within the pelvic cavity. In the latter case, the resulting abscesses are strictly circumscribed in the pouch of Douglas, and the whole inflammatory area tends to be roofed in and delimited by the omentum or small intestine. General extension of the infection into the abdominal peritoneum is unusual, and the symptoms and signs are correspondingly localized. Resolution is a frequent result; the patient recovers without operation and may regain a fair state of health. But conditions differ in puerperal salpingitis. The abdominal situation of the tubes is the cause of an abdominal as opposed to a pelvic peritonitis, since it allows the outpouring of pus among the coils of the small intestine at or just above the level of the sacroiliac joint, and herein lies the essential difference between the two varieties of salpingitis, a difference which is manifest as much in the physical signs exhibited as in the treatment required. Further, the hyperthermic condition of the uterus and appendages during the puerperium will also share in modifying the gravity of the symptoms and the rapidity of their course.

The involution of the uterus appears to be arrested in all these cases at a point at which the fundus extends about halfway between the symphysis and the umbilicus. This may be due to the presence of infection within its cavity or possibly to a neighboring active suppuration in the tubes, but the important result is that the tubes are maintained at their high level at or above the brim of the pelvis for a considerable time after the inception of the disease. Moreover, the large uterus nearly fills the pelvic cavity and affords a fixed point comparatively high up in the abdomen proper for the development of adhesions with other parts.

In the acute stage, the tubes are greatly congested and edematous, especially the ampullary portion, while the fimbriae are protruding, and the ostium is discharging pus. The isthmus may appear to be quite normal or swollen to a less extent. Any adhesions at first are light and easily separated, often being due to flakes of recent lymph and chiefly involving adjacent coils of the small intestine and part of the cecum or sigmoid colon.

The abdominal ostium frequently opens into a small abscess cavity walled in by the adherent coils and situated at first just in front of and above the sacroiliac joint. Later, when suppuration has extended, it tends to pass forward along the brim of the pelvis toward the uterine corn and is shut in from above by the omentum; or the pus may even come into relation with the abdominal wall.

19.3.1.2 Acute Salpingitis

Risk factor for acute salpingitis is an ectopic pregnancy or vice versa. Coues, of Boston, in 1911, reported a series of 214 cases of ectopic gestation in which he found that roughly 16% showed evidence of mild catarrhal salpingitis in the opposite Fallopian tube. Other etiopathogenetic factors are the same as in TOA (See sect. 19.3.2).

19.3.2 Tubo-Ovarian Abscess

During pregnancy, pelvic infection occurs quite independent of the gravid state, or the infection may exist before the pregnancy. Friedman and Bobrow have proposed four mechanisms for OA or TOA during pregnancy [68]:

- Hematogenous spread as in pelvic tuberculosis
- Lymphatic spread especially from the vagina and cervix
- Infection of an (previously) existing ovarian cyst
- A flare-up of an old infection

Similar mechanisms are described by Metzeger in 1939 [32]:

- Infection at the time of fertilization
- Infection soon after fertilization before the uterine cavity has become closed by conception (12 weeks)
- Vascular or lymphatic spread (from a septic focus in the vagina or cervix)
- A flare-up of preexisting infection
- Instrumentation sufficient to overcome natural barriers
- Ascending infection associated with threatened abortion and intrauterine bleeding

When infection occurs at the time of fertilization, attachment and detachment of gonococci to human sperm occur. The gonococcus acts as a “hitchhiker” on the traveling sperm until a favorable environment for detachment is encountered, such as may be found in the uterus or Fallopian tube [76].

19.3.2.1 In Vitro Fertilization-Embryo Transfer

Pelvic abscess formation is a rare complication of oocyte retrieval, which usually results in failure of the procedure. It is reported to occur in 0.2–0.5% of transvaginal oocyte retrievals [47, 77]. Inoculation of vaginal bacteria and anaerobe opportunists is suggested to be the cause [49]. Three different pathways for such infections are described [57, 78]:

- Inoculation of vaginal microorganisms by puncture through the non-sterile vagina
- Reinfection through puncture of chronically infected ovaries
- Infection through direct puncture of the bowel with an inflammatory or infectious spillage

There are several established and accepted techniques to decrease the risk of pelvic infection [77, 79–82]:

- The fewest possible vaginal punctures (2 max.)
- Vaginal preparation (0.5% saline or 10% povidone-iodine)
- Prophylactic antibiotics (i.v. cefazolin)

Use of prophylactic antibiotics following transvaginal oocyte retrieval is controversial as pelvic inflammation is uncommon, and these medications may not prevent all associated infections. Antibiotic prophylaxis is recommended in the risk groups for infection (see Sects. 19.3.1.1 and 19.3.1.2).

19.3.2.2 In Vitro Fertilization-Embryo Transfer and Endometriosis

Endometriosis/endometrioma is proposed to be a risk factor for PID and TOA/OA development following transvaginal oocyte retrievals [54, 55, 83]. Up to 80% of PID following oocyte retrieval had underlying endometriosis (Table 19.4) [48]. Among its risk factors, incidental aspiration of an ovarian endometrioma during the process of oocyte retrieval is believed to be a common cause for developing the pelvic infection [52, 54, 84]. The presence of old blood in endometrioma is suggested to provide a culture medium for bacteria to grow slowly after transvaginal inoculation which may explain the role of endometriosis in predisposing the patients with PID [54]. It has been suggested that both the pseudocapsule of endometrioma and its inside old blood may prevent antibiotic prophylaxis from overcoming the transvaginal bacterial inoculation [54].

Whether operative treatment of recurrent ovarian endometriosis improves the prognosis of IVF is still open [85]. Previous reports have indicated that aspiration of endometriotic cysts before ovulation induction for IVF resulted in a better clinical outcome [86]. However, pretreatment for endometrioma before IVF could potentially reduce the number of retrieved oocytes [87]. In order to prevent infection in patients with endometrioma for oocyte retrieval, it has been suggested to aspirate the endometrioma before oocyte retrieval [87]. However, these endometriotic cysts reexpand quickly after aspiration, and it is difficult to harvest some oocytes without puncturing through these chocolate cysts. In addition, the chocolate content of the follicular fluid is sometimes found incidentally after the aspiration [88].

Endometriosis is a risk factor for the development of a TOA or an OA [83], and infection-preventing measures should be applied not only prior to but also immediately after oocyte retrievals.

19.3.2.3 Pelvic Inflammatory Disease

The risk of infection is higher in cases of previous PID [37, 42, 49, 78]. Why some TOAs are

unilateral may be explained by a "flare-up" of an already preexisting but latent salpingitis [43]. This possibility would seem to necessitate either a low-grade infection of the Fallopian tube in the first instance leaving sufficient patency to permit the passage of a fertilized ovum. After nidation, the infection may then become acute probably because of the congestion produced by the gestation or unilateral salpingitis, the other Fallopian tube being patent and functioning [24]. Another proof of "flare-up" of the previous infection is an intraoperative finding of adhesions between the loops of intestine, the uterus, and the tubo-ovarian tissue indicating the chronic nature of the disease [89].

Pelvic actinomycosis is considered a genuine, albeit exceedingly rare, the hazard of IUD. In one study from the general female population, all 12 cases of OA were associated with IUD use, and some of these infections were shown to be of actinomycotic origin [21]. As an IUD-related complication of pregnancy, ovarian actinomycosis is even more exceptional [64]. Suggested pathophysiology is that the IUD causes colonization of the endometrium from where the bacteria proceed through the tube and into the peritoneal cavity, eventually gaining access to the ovarian substance at ovulation. Why actinomycotic involvement of the Fallopian tube sometimes does not occur is not clear, unless it is assumed that the dissemination of *A. israelii* is bloodborne or lymphatic rather than the result of ascending infection.

During the first half of twentieth century, tuberculous salpingitis with intrauterine pregnancy was more frequent [90] and today it is rarely seen. The frequency with which pregnancy occurs in the presence of pelvic tuberculosis is difficult to assess for the following reasons: (1) the incidence of unsuspected pelvic tuberculosis in apparently healthy females is unknown; (2) pelvic tuberculosis may be first discovered after pregnancy has occurred; (3) in proved cases of pelvic tuberculosis, pregnancy has rarely been reported.

19.3.2.4 Puerperium

Puerperium appears to be the least likely time to develop a TOA because ascending infection, which is the major pathophysiology in developing PID in most women, rarely occurs during this phase. The coexistence of vaginal colonization and delivery has been associated with severe infections, such as endometritis, salpingitis, and TOA [91]. Vaginal *S. pneumoniae* colonization present during CS and neither the antenatal administration of amoxicillin, given for group B *Streptococcus* prophylaxis nor intraoperative prophylaxis with cefazolin were sufficient to prevent maternal and neonatal infection [92].

19.3.2.5 Tubal Sterilization

Particularly in women who have had tubal sterilization, the incidence of TOA is minimal because the procedure blocks communication between the genital tract and the pelvic cavity [93]. Theoretically, this blockage should prevent an ascending transmission of any organisms, if present, from the genital tract proximal to the site of tubal sterilization into the peritoneal cavity. This view is supported by clinical evidence that a complete or even partial occlusion of tubes appears to lessen the severity of infection when it occurs [93]. Three possible explanations of TOA after previously occluded tubes have been proposed [93]:

- Persistent tract or reconnection between the two tubal segments
- Factors related to the operative procedure
- Systemic factors such as a hematogenous or lymphatic bacterial spread with an immunocompromised state

Time intervals from tubal occlusion to TOA range widely, from as early as 36 h to up to 12 years [93].

19.3.2.6 Genital Anomalies

Structural genital anomalies are documented risk factors for the development of pelvic abscess during pregnancy [37, 38, 94]. It is not known whether anomalies per se are the risk factor or invasive procedures directed to correct these anomalies or to enable pregnancy are the real cause of the pelvic abscess.

19.3.2.7 Infective Non-gynecologic Etiology

The etiologies may include infective non-gynecologic conditions such as ruptured colonic or Meckel's diverticulitis or acute appendicitis (Table 19.5); it is not specified whether the abdominal operation per se is a risk factor [37, 38] or operation due to intra-abdominal infective cause results in infective complication [95], such as TOA. Even TOA of unknown origin has been reported [12].

19.3.3 Ovarian Abscess

An OA is defined as a primary infection of the ovary without the involvement of the Fallopian tube, whereas a TOA involves both the Fallopian tube and the ovary.

> The ratio of ovarian to tubo-ovarian abscess is increased in pregnancy [40].

The possible factors for the cause of OA are disruption of the ovarian capsule, giving bacteria access to the ovarian stroma, and hematogenous and lymphatic spread [21]. Nevertheless, the most common mechanism is considered to be an alteration of the ovarian capsule at the time of ovulation or by penetration during surgery or surgical procedures. Patients who suffer from OA almost always have a history of salpingitis, endometriosis, pelvic adhesions, hydrosalpinx, or pelvic surgery [49, 54].

The interval between capsule disruption and clinical presentation may vary, depending on the bacterial inoculum dose, type of bacterium, its virulence, and whether the infection occurred secondary to a direct contamination at surgery or spread through devitalized tissue, most commonly after vaginal hysterectomy, ovarian cystectomy, CS, during pregnancy, the use of an IUD [21, 96], or transvaginal/percutaneous needle aspiration of an endometrioma [52, 97]. Nevertheless, despite the advantages of image-guided vaginal oocyte collection, there are some inherent risks, such as injury to blood vessels and hemoperitoneum, trauma to pelvic organs, infection or exacerbation of PID, rupture of endometriotic cysts, ureteral lesions, and hyperstimulation [50, 98–100].

Table 19.5 Differential diagnoses of pelvic inflammatory disease in pregnancy

Gynecologic/obstetric	Non-gynecologic
Ectopic pregnancy	Perityphlitic abscess
Threatened abortion	Colonic diverticulitis
Endometrioma	Meckel's diverticulitis
Adnexal torsion	Acute appendicitis
Hemorrhagic cyst	Urinary tract infection
Ovarian hematoma	Iliopsoas abscess
Ovarian vein thrombosis	Crohn's disease
Placental abruption	Urolithiasis
Chorioamnionitis	
Pelvic neoplasm	
Uterine horn abscess	

OA after transvaginal oocyte retrieval or transcervical embryo transfer occurs in 0.2–2.2% [47, 49, 50, 101]. Risk factors include (1) ovarian and/or pelvic endometrioma (most common) [42, 57, 55, 52], with old blood providing a rich culture medium for bacterial proliferation [78]; (2) previous (operated or non-operated) ectopic pregnancy [59, 53]; or (3) follicle aspiration even without any subtle pelvic pathology [50].

The etiology of OA in pregnancy is uncertain and in all probability is different from that in the nonpregnant state. Ascending infection is the most important mode of infection in nonpregnant women. Barriers to ascending infection in pregnancy include cervical mucus plug, intact fetal membranes, and the decidua covering the openings of the Fallopian tubes. There are several classifications and mechanisms [68, 102] proposed for infection of ovaries during pregnancy (see Sect. 19.3.2). Data that confirm these facts are that OA readily occurs in the puerperium if there is an infection of the birth canal during or following parturition. Also, it is likely that the ovary becomes infected quite independently of the gravid state or that the infection exists before the pregnancy. During the last decades, the more common cause is oocyte retrieval as a part of IVF pregnancy (see Sect. 19.3.2.1) [45, 55, 58].

19.3.4 Intramyometrial Abscess

The etiology in one published report of two cases is failed instrumental delivery in the second stage of labor [73].

19.4 Microbiology

Bacterial confirmation of pelvic infections is rarely available after transvaginal punctures including even *E. coli* [103] and a subclinical infection with *C. trachomatis* [104] and rare isolate in general population *Atopobium vaginae* [105], *S. aureus*, and mixed anaerobic bacteria [55]. Anaerobic opportunists of the vagina are found to be etiological agents in pelvic abscesses after transvaginal oocyte retrieval. *E. coli*, *B. fragilis*, *Enterococcus* spp., and *Peptococcus* spp. are common [49, 50]. There are also case reports with other microorganisms such as *Fusobacterium necrophorum* during puerperium [106]. TOAs are usually polymicrobial; organisms isolated from TOAs seem to belong to the facultative anaerobe *Enterobacteriaceae* family (*E. coli, Proteus* spp., *Klebsiella* spp.) and anaerobic *Peptostreptococcus* spp., *Streptococcus* spp., or *Actinomyces* spp. in nonpregnant women [37, 43, 64, 107, 108].

During the first half of the twentieth century, tuberculous salpingitis with intrauterine pregnancy was more frequent [90] and today it is rarely found.

19.5 Clinical Presentation

19.5.1 Suppurative Salpingitis

19.5.1.1 Acute Suppurative Puerperal Salpingitis

Today fully developed a clinical presentation in advanced stages is not commonly seen due to the modern diagnostic imaging modalities used early in the course of the disease. Clinical presentation of all stages of acute puerperal salpingitis was described by Aleck W. Bourne in 1921 [75]. It differs in many aspects from that of nonpuerperal origin. Essentially, the tubes are abdominal and not pelvic organs, and they are usually affected before they have reached their normal positions in the pelvic cavity. Like acute appendicitis, pain precedes everything and is rapidly followed by a slowly rising temperature becoming 38.9–39.4 °C on the third or fourth day, with a pulse the following suit. Vomiting is not a feature in the early cases. An interesting and indicative symptom, occasionally present, consists in retention of urine or painful micturition. This is especially seen in cases in which a cellulitis has developed secondarily to the salpingitis involving the upper part of the broad ligament and extending forward beneath the round ligament to the neighborhood of the bladder. If the patient is not operated upon, there is a persistent fever with chronic pain and wasting.

In the early stages, the abdomen is not truly rigid, and there is nothing but tenderness fairly accurately localized to a point about 2 in. below and external to the umbilicus – i.e., over the posterior part of the lateral brim of the pelvis. The uterine fundus can be felt rising about 5 cm above the symphysis. It may or may not be tender at first, but later it becomes so, especially if adhesions become attached to the uterine corn or if a secondary cellulitis develops.

After a week or more, it is not unusual to find a mass in the hypogastrium to one side of the uterine fundus. Except for cellulitis, which is felt immediately above Poupart's ligament, such a tumor is nearly always due to adherent omentum and coils of the distended gut. Later, as suppuration spreads, there is true rigidity and tenderness of the whole hypogastrium, with extension upward over the ovarian veins, if thrombosis of these vessels has taken place.

By way of the vagina, the signs are difficult to appreciate, for the primary changes are not in the pelvis and the gentlest manipulation causes pain. The uterus can be felt enlarged, with limited mobility soon developing and later complete fixity. In the first few days, it is symmetrically disposed of in the pelvis, but later it may be displaced laterally by secondary cellulitis, and the displacement is toward the side which is affected.

During the first week, there may be little or nothing felt in the lateral fornices, but later an indefinite tender mass can be felt very high up in the posterolateral region which is largely made up of the ovary surrounded by adherent coils enclosing pus. The accessible part of Douglas's pouch seldom, if ever, contains anything, though by the vagina the posterior portion of the lower part of

the uterine body may give the impression of a tumor because it tends to bulge backward immediately above the cervix. By far the best palpation of the pelvis is obtained by rectal examination. High up on one or both sides, the early composite swelling can be made out fairly early, becoming larger and more distinct as time passes.

A swelling high up in the broad ligament disturbing the position of the uterus is probably a mass of secondary cellulitis.

Classic clinical presentation of TOA is abdominal pain, cervical motion tenderness, and adnexal tenderness, as well as one of the following:

- Fever >38 °C (101 °F)
- Abnormal cervical discharge
- Elevated ESR or CRP or positive cervical cultures for *N. gonorrhea* or *C. trachomatis*

19.5.2 Tubo-Ovarian Abscess

Pregnancy is said to protect against pelvic infections. Clinicians are therefore unlikely to suspect a pelvic abscess as a cause of an acute abdomen in pregnancy. A detailed history should search for [63, 64]:

- Previous episodes of PID
- Unexplained spontaneous abortions
- Intrauterine device

Clinical presentation between ruptured and unruptured TOA differs. In unruptured cases, the first signs of the disease are sometimes mild and not specific, and the findings may be altered significantly by the size of the gravid uterus [38, 54]. Recurrent symptoms of abdominal or pelvic pain in the postoperative period and interpregnancy period suggest the chronic nature of the disease. However, the courses of antibiotics and the low virulence of the organisms result in chronic pelvic infection. History of pelvic pain can be present for several months or years [11]. A history of PID is present in only 50% of patients. The infection may flare up and present any time during pregnancy. Pain is mostly gradual in onset, but it finally had become so severe that the patient is unable to be out of bed. While at rest, intermittent cramping, much like menstrual cramps, could be present. There are no gastrointestinal symptoms [11]. There is no vaginal bleeding and the membranes are intact, but cervical discharge is often present [94]. Patients with TOAs typically present with a history of pelvic or abdominal pain and fever. A significant proportion of women with TOA is afebrile [11] (and many of these have normal WBC counts) [2].

During the abdominal examination, a suprapubic or low abdominal mass could be found. It can be mildly tender with cystic consistency. Vaginal tenderness during palpation of the fornix is elicited on the side of abdominal pain [27]. If no classical clinical features of acute peritoneal or pelvic infection are present, mostly it is not suspected preoperatively and can be found only during emergent or elective CS [109]. In ruptured cases, peritonitis is present and the patient is febrile, sometimes vomiting [12].

If the TOA is localized, pelvic mass can be found (it could be a hydrosalpinx, tubo-ovarian complex, or other complex adnexal mass). If the TOA ruptures, generalized tenderness over the entire uterus could be elicited. The uterus is very irritable and minimal stimulation produced contractions. Guarding on the side of the rupture is present. If rupture has occurred, peritonitis may lead to septic shock. Pelvic examination usually reveals extreme pelvic tenderness (cervical motion tenderness), and mass may be present. Cervix is closed if there are no signs of preterm labor. Per vaginam, there can be some evidence of a previous gonorrheal infection as shown in the swelling of the Bartholinian orifices and granulation of the vaginal mucosa [26].

A pelvic infection becomes clinically evident within hours up to a few days after oocyte retrieval. The time from oocyte retrieval to the manifestation of a frank pelvic abscess is much longer. Diagnosis of PID after IVT-ET mostly occurs within the first week after the procedure [47–49, 54] and in less than 25 days in almost half of the patients [45]; however, prolonged intervals of 56 days have also been reported (Table 19.4)

[57, 54, 55, 58]. PID after IVT-ET with underlying endometriosis is based on the same signs of peritonitis on physical examination, cervical and adnexal tenderness, the rise of body temperature to >37.8 °C for 48 h, cervical discharge, WBC count >12,000/μL, and elevated ESR.

19.5.3 Ovarian Abscess

Clinical presentation depends if the abscess is unruptured or ruptured. Women with OA during pregnancy may present with a wide range of clinical symptoms with an unruptured abscess. Partly, clinical presentation depends on the type of the bacteria, a load of the bacteria, whether the infection in mono- or polymicrobial, and immune status of the patient. Most cases (with or without subsequent pregnancy) present with indolent onset of abdominal or pelvic pain [57]. The interval between TVOR and symptom onset is generally short but highly variable and occasionally prolonged (mean, 38.5 days; median, 22.5 days; range, 1–320 days) [57]. If pregnancy followed TVOR, OA developed within 4 weeks in 50% of patients and the remaining 50% after these 4 weeks up to postpartum period [57]. (Low-grade) fever is present in 95% of patients [45, 57], but may be the only presentation in 50% of cases.

Detailed history is important and the risk factors are the same as for TOA (see Sect. 19.5.2). Palpable mass can be detected. On speculum examination, the cervix and vagina were healthy. A woman with a ruptured OA presents with features of diffuse peritonitis [64]. In cases with impeding rupture, diffuse lower abdominal pain may worsen to severe pain associated with anorexia, nausea, and vomiting in case of rupture.

19.6 Differential Diagnosis

Table 19.5 summarizes gynecologic and non-gynecologic causes of inflammatory conditions in the pelvic region and lower abdomen. Differential diagnosis is somewhat different between early (ectopic pregnancy, threatened abortion, etc.) and advanced (placental abruption, chorioamnionitis, ovarian vein thrombosis, etc.) pregnancy. Ovarian vein thrombosis is described in the Sect. 1.6.7.3. Sometimes it is difficult to differentiate between types of PID, such as TOA and uterine horn abscess.

19.7 Diagnosis

Before the widespread use of ultrasonography, preoperative or prelabor diagnosis was rare. English literature of 19 cases up to 1977 found that in only one case (5.3%), the diagnosis was made preoperatively [37]. In most cases, the diagnosis was made during emergent CS when complicated PID was found as a cause of fetal distress, preterm labor or preterm premature rupture of membranes [109], or symptoms and signs of acute abdomen.

19.7.1 Laboratory Findings

When OA is the underlying cause, leukocytosis is common (100% of cases in which it was reported), and the erythrocyte sedimentation rate and CRP were elevated when measured [45, 57].

19.7.2 Abdominal Ultrasound

Abdominal ultrasonography should be the first diagnostic imaging modality for suspected PID. This modality is readily available and non-invasive and can be performed at the patient's bedside [13, 110]. Transabdominal sonography (TAS) might not be as useful in late gestation when enlarged uterus interferes with adequate compression of the abdominal wall with the probe. Transvaginal sonography (TVS) allows detailed visualization of the uterus and adnexa, including the ovaries. The Fallopian tubes are usually imaged only when they are abnormal and distended on physical examination, primarily from postinflammatory obstruction. TAS is complementary to the TVS because it provides a more global view of the pelvic contents

(Fig. 19.3) whether TAS (bladder filling required) or TVS (bladder filling not required) is performed first and whether the complementary examination is needed for a final diagnosis is a matter of individual clinical imaging practice [110, 111]. The free fluid in the abdomen indicates a high probability of ruptured TOA. The sensitivity of ultrasound for the diagnosis of TOA of 56–93%, with a specificity of 86–98% [111]. The wide range is likely due to differences in methods, including variability in the technology used (TAS vs. TVS), the person performing and interpreting the ultrasound (radiologist vs. gynecologist), the study population (patients with suspected PID and patients with a palpable adnexal mass and suspected PID vs. only patients eventually requiring laparoscopy or surgery in the workup of their PID), the study design (retrospective vs. prospective), and interpretation of positive results (inclusion of any adnexal mass vs. limiting it to those specifically diagnosed as abscess) [111].

19.7.3 Abdominal CT

Abdominal CT scan is avoided by most clinicians during pregnancy. But during the postpartum period, when MRI is not available, CT is commonly performed when TOA is suspected (Fig. 19.4).

19.7.4 Abdominal MRI

Abdominal MRI serves as an excellent imaging modality when ultrasonographic findings are equivocal (Fig. 19.5). Abdominal MRI is more accurate than abdominal ultrasonography in the diagnosis of PID in general female population. The sensitivity in the diagnosis of PID is 95%, the specificity 89%, and the overall accuracy 93%. For TVS, the corresponding values are 81%, 78%, and 80% [112].

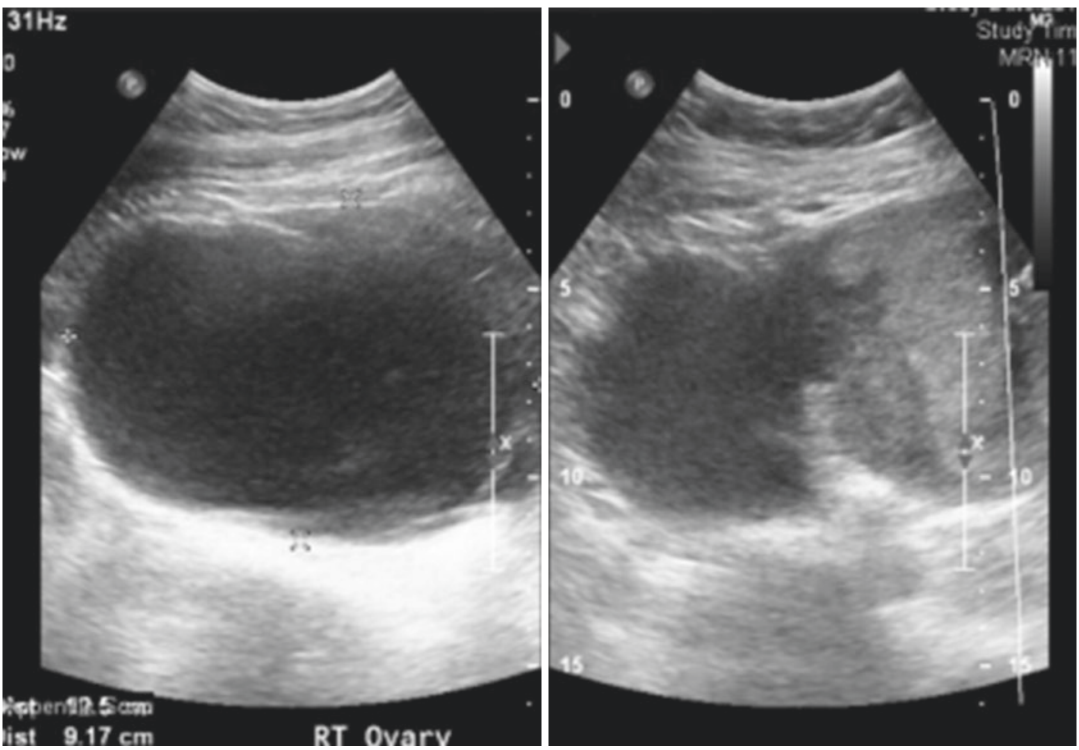


Fig. 19.3 Transabdominal ultrasonography. A 12.5-cm-sized right ovarian cyst in pregnant women. Reproduced with permission from [44]

Fig. 19.4 Abdominal CT scan of right tubo-ovarian abscess, 18 days post-Cesarean section (*arrow*). Reproduced with permission from [92]

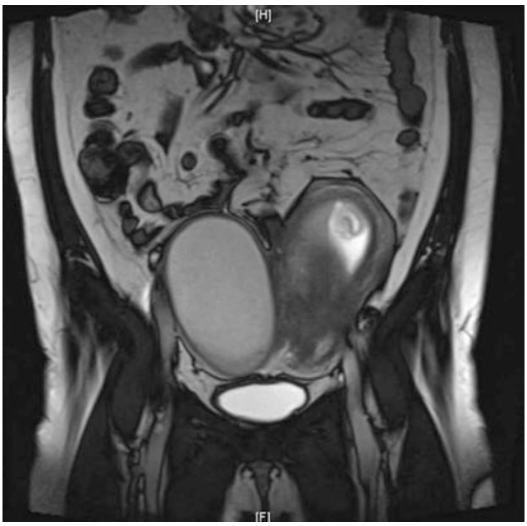


Fig. 19.5 Abdominal MRI (T2-weighted image). Right ovarian cyst and intrauterine pregnancy. Reproduced with permission from [44]

19.7.5 Bacterial Cultures

In general female population, approximately one-third of the cultures from culdocentesis and Fallopian tube exudates are sterile in patients with acute PID [113–115]. Reasons include recurrent salpingitis, which results in the destruction of the tubal architecture obstructing passage of the organisms into the peritoneum and intracellular organisms (e.g., *Chlamydia)* that are not isolated from exudates. Improper culture techniques for viruses, *Chlamydia* spp., etc., are included.

The positive endocervical culture for *N. gonorrhoeae* should serve as a reminder that there is a relatively high frequency (6%) of asymptomatic gonorrheal infection in the pregnant population [115].

> Routine endocervical cultures should be obtained in all pregnant patients on initial evaluation with suspected or proven (pyo) salpingitis.

19.8 Prevention of Infection

19.8.1 Preprocedural Elimination of Endometriosis

Endometriosis may be a predisposing factor for oocyte retrieval-induced PID (see Sects. 19.3.2.1 and 19.3.2.2). In regard to the few investigations available, it is rather soon to conclude a management protocol. However, some precautions may be useful for cases with endometriosis that undergo oocyte retrieval. Full evaluation and removal of endometrioma should be considered for the patients undergoing IVF [42]. However, non-vaginal methods of oocyte recovery like transabdominal approach in cases with endometriosis and pelvic adhesion seem preferable.

19.8.2 Procedural Vaginal Antisepsis

Traditionally, the vagina is not prepared with antiseptic solutions (e.g., aqueous povidone-iodine) before oocyte retrieval since these agents are considered to be embryotoxic. Therefore, employing only normal saline irrigation of the vagina is usually the norm prior to oocyte retrieval. However, most believed that using only normal saline rinsing and irrigating the vagina canal can only wash away the vaginal discharge without destroying potentially harmful bacteria preexisting in the vaginal flora. By applying an additional antiseptic solution followed by a normal saline solution, one can eliminate most if not the entire vaginal flora. This process would not jeopardize the development of the oocyte because

all the antiseptic solution has been completely flushed away before oocyte retrieval [88].

19.8.3 Prophylactic Antibiotics/Antifungal Agents

Older studies question prophylactic antibiotic use given the low incidence of pelvic infections [77, 82, 101]. Others, however, do advocate using prophylactic antibiotics as a general rule [50, 79, 80]. Although there is no consensus on the type and protocol for antibiotic use, doxycycline and metronidazole are the most common. First-generation cephalosporins, which are routinely used as prophylactic antibiotics preoperatively, are another class of antimicrobials that have been used before TVOR [57]. Some even recommend fluconazole, an antifungal agent, as part of their protocol prior to oocyte retrieval [79], due to several *Candida glabrata* infections diagnosed in the second half of gestation following IVF [116]. The yeast was isolated from both the mothers and their babies. Another approach can also be to reserve prophylactic antibiotics to high-risk patients such as those with a history of PID or endometriosis. Patients who develop OAs almost always have a history of salpingitis, endometriosis, pelvic adhesions, hydrosalpinx, or pelvic surgery [49, 50]. Prophylactic antibiotics during oocyte retrieval are recommended in these groups of patients with increased risk [49, 54].

19.9 Treatment

19.9.1 Medical Treatment

19.9.1.1 Tubo-Ovarian Abscess

A *minor* pelvic infection, found in 0.3% of cases, is defined by pyrexia and pelvic tenderness with no evidence of abscess formation on ultrasound. In these cases of the early course of infection, patients can be treated with antibiotic therapy [13, 49]. More severe infections leading to TOA also occurred in 0.3% of cases [47, 49]. Unruptured pelvic abscess or TOA may be given supportive care and treated by preoperative broad-spectrum intravenous antibiotics effective against gram-positive, gram-negative, and anaerobic bacteria for at least 72 h before operative intervention is indicated. There are no guidelines addressing earlier operative intervention after reproduction assisted procedures, and the possible worse outcome has not been documented.

Catheter drainage of a TOA can be done percutaneously under ultrasound or CT control [38, 117]. One should be cautious of peristaltic bowel on ultrasound to avoid bowel puncture and subsequent inflammation/infection/peritonitis.

19.9.1.2 Ovarian Abscess

The optimal management of TVOR-related OA during pregnancy (and in general female population) is unclear. Ruptured OA with resultant peritonitis clearly requires urgent surgical intervention. Whether drainage should be delayed in more stable clinical settings is uncertain. Intravenous antibiotics effective against gram-positive, gram-negative, and anaerobic bacteria should be administered. The easier spread of infection is present in advanced pregnancy when ovaries are out of the pelvis.

19.9.2 Surgical Treatment

19.9.2.1 Indications

Surgical treatment was performed in 88% of pregnant patients with TOA [42], indicating that surgical intervention is usually necessary. In general female population, ultrasonographic TOA morphology cannot predict the necessity for operative treatment [118]. Indications for surgical therapy in both TOA and OA are:

- No response to antibiotics within 72 h
- Abscess rupture or adjacent organ rupture
- Surrounding organs affected by the inflamed mass
- Unsuccessful drainage of the abscess
- Uncooperative patient for percutaneous drainage
- Uncertain diagnosis

19.9.2.2 Operative Principles

As most of the patients are young, conservative surgery should be attempted if the pathology is limited to one adnexa [12].

Pregnant women with unilateral involvement managed with the preservation of the contralateral ovary and the tube have had a favorable outcome [11, 12, 37, 66, 107, 119]. There are two surgical abdominal access options available: laparoscopy and laparotomy. Surgical drainage of OA and conservative surgical approach with antibiotics should be the first-line therapy albeit there is no consensus on management [57, 120]. Drainage can be performed: (1) percutaneously, (2) through culdotomy, or (3) using laparoscopy with peritoneal lavage (Fig. 19.6) [44, 45, 56, 91]. Sometimes it is possible to drain the abscess by laparoscopy, but severe pelvic adhesions secondary to abscess formation can prevent completion of the laparoscopic procedure, and then conversion to laparotomy is indicated. Percutaneous, laparoscopic, transvaginal, and surgical drainage have all achieved good results. The possible catheter-based therapy failure could be present if delivery would occur before complete drainage of the abscess. In these conditions, the catheter might dislodge from the abscess during postpartum uterine involution when the ovary would be drawn back into the pelvis. For nonurgent conditions, the second trimester of pregnancy has classically been considered as the safest period for surgical intervention.

In severe cases where the one-sided adnexal disease is present, isolated resection of the Fallopian tube [27], unilateral salpingo-oophorectomy [89], or even hysterectomy with bilateral salpingo-oophorectomy could be done [98]. Hysterectomies are more commonly performed among multiparous patients [121]. Patients without adnexa are still able to conceive via IVF-ET.

19.9.3 Anesthetic and Perioperative Management

See Chap. 21.

19.9.4 Obstetric Management

19.9.4.1 Prevention and Treatment of Preterm Labor

See Chap. 23.

19.9.4.2 Mode of Delivery

Despite intraperitoneal inflammation/infection in a form of complicated PID, there are cases with term delivery after successful surgical [108, 122] or antibiotic [123] treatment during pregnancy.

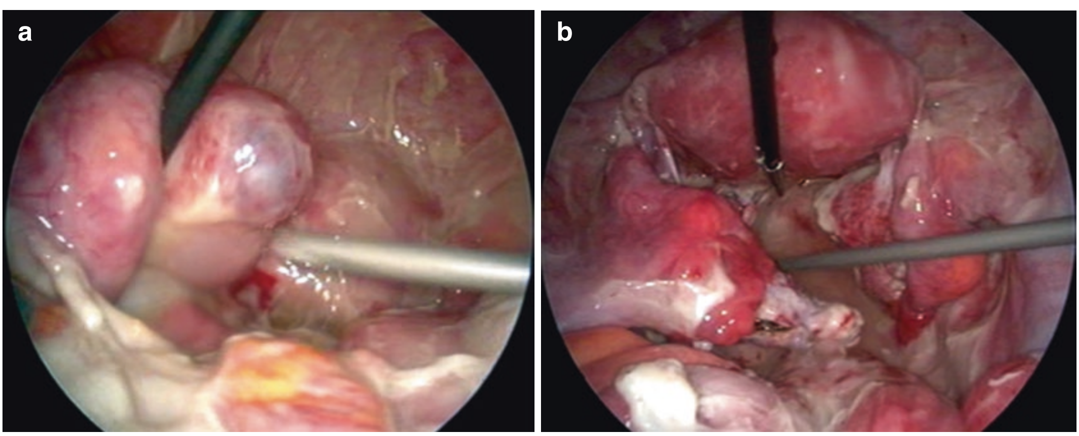


Fig. 19.6 (**a**) Laparoscopic image of the pelvis, depicting a left ovarian mass consistent with abscess, disseminated purulent fluid. (**b**) Appearance after excision of the mass and irrigation of the pelvis. Reproduced with permission from [45]

19.10 Prognosis

19.10.1 Maternal Outcome

19.10.1.1 Tubo-Ovarian Abscess

Even in the beginning of the twentieth century with more cases of pelvic tuberculosis during pregnancy, maternal survival was excellent [124]. Currently, with completely changed underlying microbial flora causing complicated PID in pregnancy, the maternal outcome is still excellent as in general female population with survival approaching 100% [45, 125]. Delay in diagnosis and treatment especially with ruptured TOA causing peritonitis increases the possibility of maternal mortality and morbidity [38]. There is fertility impairment following TOA, given that the tubes are involved in the disease [126].

19.10.1.2 Ovarian Abscess

Tenani, in 1921, reported the rupture of a pyoovarium during the second stage of labor, which was followed by maternal streptococcic peritonitis and death [62]. Currently, maternal survival is 100% [63, 64].

19.10.2 Fetal Outcome

During pregnancy, *S. pneumoniae* has been associated with chorioamnionitis and neonatal infection. Transmission might occur: (1) transplacentally during maternal bacteremia, (2) as ascending infection from the maternal genital tract, (3) intrapartum while passing through the colonized birth canal, or (4) through respiratory tract contamination in the early postpartum period [127]. Neonatal mortality (there are no isolated results for PID) ranges 10.3–50%, and it is also associated with high morbidity, such as neurological sequelae [128, 129]. Neonates can develop early- or late-onset sepsis and often have no obvious perinatal risk factor [129]. Reasons for increased number of pneumococcal neonatal sepsis recently may be (1) increased rates of genital *S. pneumoniae* colonization due to changes in sexual practice (i.e., increased oro-genital sex), (2) improved laboratory isolation techniques, (3) the increased use of antimicrobials for prevention of group B streptococcal disease selecting for more resistant pathogens such as *S. pneumoniae* [130], and (4) publication bias with positive cases being published more frequently [128].

Fruhinsholz and Feuillade in 1924, in their classical paper dealing with utero-adnexal tuberculosis and pregnancy, referred to cases reported by various observers of normal pregnancy following conservative surgery for pelvic tuberculosis [124]. Today, pelvic tuberculosis in pregnancy is extremely rarely reported.

19.10.2.1 Acute Salpingitis

Previously prognosis for the fetus was poor. Up to 1993, the average gestational age at diagnosis was approximately 12 weeks; 27% of patients reached term pregnancy and delivered; 40% resulted in spontaneous abortions, 13% in stillbirth, and 7% in premature delivery with fetal death [131].

19.10.2.2 Tubo-Ovarian Abscess

Several possible explanations for the role of infection in reducing pregnancy success have been suggested especially during IVF-ET pregnancy with PID. Introducing endotoxin-releasing bacteria into the peritoneal cavity during transvaginal oocyte retrieval may induce abortion by promoting the release of prostaglandins as well as catecholamines and cortisol which play some role in the termination of pregnancy. Moreover, local inflammatory reaction and fever may also affect the success rate of pregnancy [132]. Due to the adverse effect of endometriomas on IVF outcome, it is suggested that endometrioma should be removed in patients with endometriosis prior to IVF admission. Preconception evaluation and treatment should be considered for such condition [42].

In cases when surgery was performed before delivery, the pregnancy was terminated shortly after surgery in 35% [42]. Loss of the pregnancy occurred in 90% of cases with TOA developing before 24 weeks of gestation [42]. The fetal survival rate of those pregnancies complicated by a TOA late in the second trimester was approximately 33% [37, 133]. There are cases with term pregnancy after conservative treatment [134].

19.10.2.3 Ovarian Abscess

When OA was the underlying cause, fetal mortality depends on many factors, and different authors have different survival. Some claim extremely low fetal survival with live cases delivered prematurely with severe fetal complications [38, 45, 57]. Others claim excellent survival of healthy newborns [63, 64].

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Part III

Additional Considerations

20 Urologic Emergencies

Abstract

Urologic causes of acute abdominal pain in pregnancy are frequent. It is important to define the diagnosis preoperatively because the majority of urologic emergencies are treated conservatively. Physiologic ureteric dilation has right-sided predominance with more than 80% of cases, and some of these patients are operated due to the misdiagnosis of acute appendicitis in pregnancy. The most common causes of urologic emergencies are urinary tract calculi and acute pyelonephritis. Successful treatment of both conditions is nonoperative in the vast majority of patients. If the patient presents with urinary tract obstruction, it is important to determine the level and the cause of urinary tract obstruction. Modern imaging modalities help in accurate diagnosis and determination of the level of obstruction. This is important because for some causes only nonoperative or minimally invasive percutaneous or endoscopic procedures are necessary for successful resolution of obstruction. Other conditions such as renal parenchymal rupture, renal artery aneurysm rupture, or intraperitoneal bladder rupture commonly require fast invasive radiologic or operative intervention.

20.1 Anatomic and Functional Changes of the Urinary Tract During Pregnancy

20.1.1 Upper Urinary Tract

Upper urinary tract dilatation in pregnancy is a phenomenon described for more than 200 years. In a normal pregnancy, the kidneys elongate ≈1 cm because of the increase in vascular volume and interstitial space/fluid [1]. Nearly all pregnant women will have by term detectable asymptomatic hydronephrosis [2], but only a small proportion will progress to anuria, urinary tract rupture, or renal failure.

20.1.2 Lower Urinary Tract

During pregnancy, especially advanced pregnancy, the urinary bladder is compressed at its dome (Fig. 20.1). Intravesical pressure increases from 9 to 20 mm H_2O with a corresponding increase in urethral closure pressure [3]. Cystoscopically, an indentation of the bladder dome by the enlarged uterus is visible during pregnancy, and the ureteric orifices are visualized in a higher position than in the nonpregnant state [4]. During fluoroscopy, alterations in the bladder

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_20

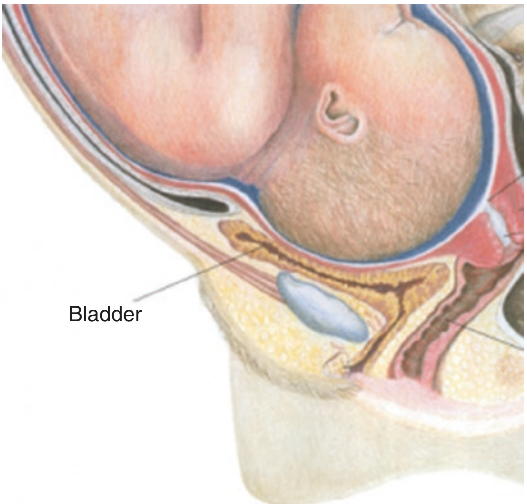

Fig. 20.1 Schematic presentation of urinary bladder compression by fetal head in advanced pregnancy. Reproduced with permission from [9]

profile are present (Fig. 20.2). Vaginal delivery is accepted as a major factor predisposing women to prolapse of the pelvic organs [5], including loss of support for the anterior vaginal wall and bladder. Also, it is not vaginal delivery alone, but also pregnancy itself that is associated with increased mobility and descent of the bladder and other pelvic organs. At term, the bladder neck descends with Valsalva approximately 5 mm more in pregnant women than in nonpregnant controls [6], and almost half of primiparous women have pelvic organ prolapse stage II (the leading edge of the vaginal walls or cervix come to at least within 1 cm of the hymen) [7, 8]. The descent of the anterior vaginal wall and bladder to the level of the hymen by the third trimester of pregnancy can be treated as a normal occurrence in pregnancy, is usually asymptomatic, and usually, resolves after delivery. As such, the presence of anterior vaginal wall descent or "cystocele" in this setting does not merit investigation or treatment.

20.1.3 Composition of the Urine

The causes of urolithiasis are the anatomic and physiological changes observed in pregnant women in the structure of the urinary system and in the chemical properties of urine. These changes are summarized in Table 20.1.

20.2 Symptomatic Urinary Tract Stones

20.2.1 Incidence

The urinary stone disease affects 10% of the population in a lifetime. The increase in this rate in the last decade is attributed to the developing imaging methods and more frequent use of imaging as well as to dietary habits, changing climate conditions, increasing obesity, and diabetes mellitus ([12–15]). Although urinary stone disease is used to be more widespread among men, the difference between genders disappeared with the increase of urinary system stone incidence in women ([15, 16]). Urinary stone disease is observed in 1/200–1/2000 pregnancies [17, 18], but there is no difference in prevalence between pregnant and nonpregnant groups of similar age [19, 20].

20.2.2 Etiopathogenesis

As previously stated, the etiopathogenesis is connected with changing dietary habits, changing climate conditions, increasing obesity, and diabetes mellitus [12–15]. Anatomic and physiological changes during pregnancy influence the chemical properties of urine. Increasing progesterone causes relaxation in the smooth muscles of the urinary system. An additional factor for dilation and stasis occurs as a result of mechanical pressure from the fetus on the urinary system. Increasing glomerular filtration, calcium supplement treatments and increased vitamin D level increase calcium excretion in the urine [21–23]. Furthermore, uric acid, sodium, oxalate, and other lithogenic factors show an increase during pregnancy [22, 23]. Calcium phosphate stones are observed in 75% of the pregnant women, whereas in general population, calcium oxalate stones are usually present [20, 24, 25].

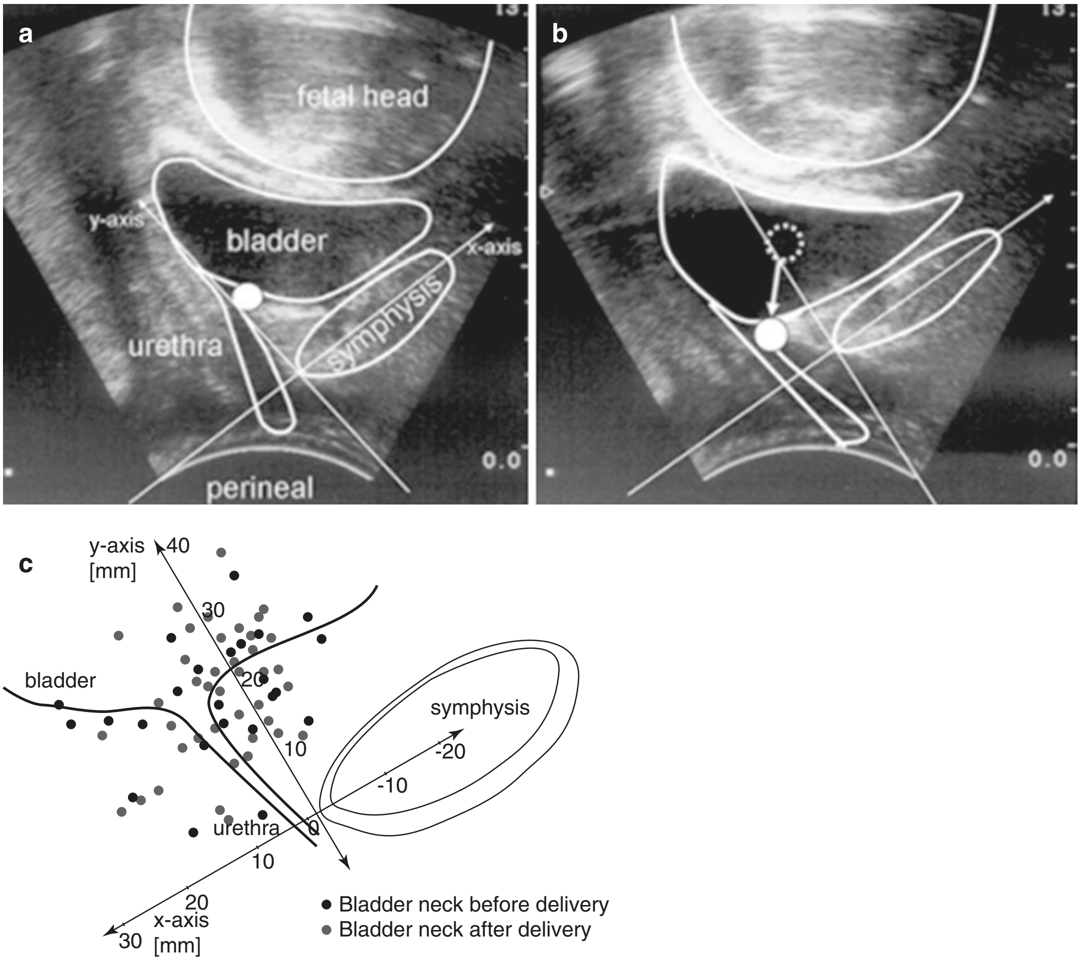

Fig. 20.2 Bladder neck at rest (**a**) and with Valsalva maneuver (**b**); point indicates the bladder neck and arrow as a vector for the bladder neck mobility; (**c**) position of the bladder neck before and after delivery at rest (reproduced from [10] under the open library I. Holzapfel Publishers)

Table 20.1 Physiological changes in the kidney occurring during pregnancy (reproduced from [11] under the CC BY 3.0)

Stone-inducing factors	Stone inhibitor factors
Increased renal blood flow, leading to a 30–50% rise in glomerular filtration rate	Increased excretion of citrate, magnesium, glycoproteins, uromodulin, and nephrocalcin (increased glomerular filtration rate)
Increased filtered loads of calcium, sodium, and uric acid	
Hypercalciuria enhanced by placental production of 1,25(OH)$_2$D$_3$, which increases intestinal calcium absorption and secondarily suppresses PTH	
Hyperuricosuria has also been reported as a result of increased filtered load of uric acid	

20.2.3 Clinical Presentation

The most common signs/symptoms are a flank pain (89%) and microscopic hematuria (95%) [17]. In asymptomatic patients, both colicky pain and hematuria may be absent because of the physiological dilated hydroureter.

20.2.4 Differential Diagnosis

Differential diagnosis of symptomatic upper urinary tract stones is similar to the pyelonephritis in pregnancy (see Sect. 20.3.4). Commonly, the pain is severe and acute in nature, so additional differential diagnoses

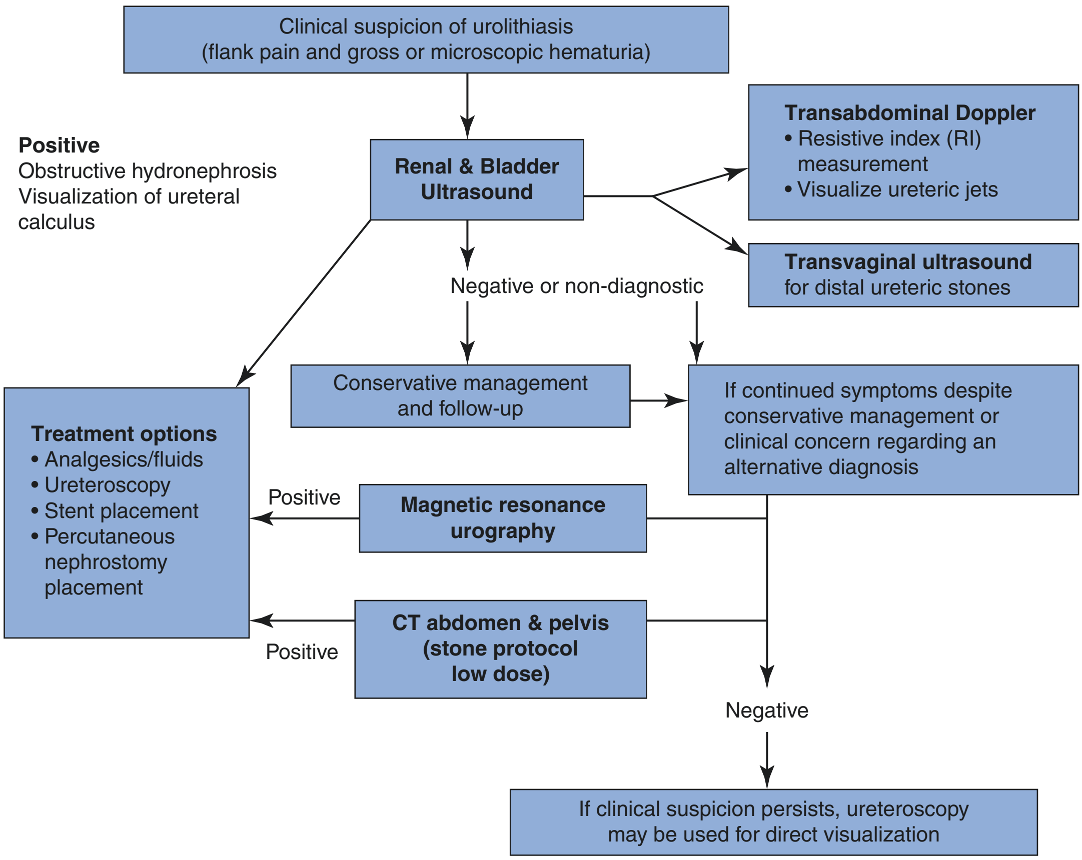

Fig. 20.3 Diagnostic algorithm for pregnant patients with suspected urolithiasis. Reproduced with permission from [28]

include vascular etiology: ruptured renal artery aneurysm (see Sect. 20.7), renal vein thrombosis, and renal infarction.

20.2.5 Diagnosis

The rate of negative ureteroscopy in pregnant women is 14% [26]. Since the physiologic dilation can be misdiagnosed as obstruction by a stone of the distal part of the ureter, the role of imaging methods becomes prominent to avoid invasive procedures based on false positive and the complications that could occur as a result. The diagnostic algorithm is presented in Fig. 20.3.

20.2.5.1 Laboratory Findings

In pregnancy, recommendations for the evaluation of nonpregnant population by *American Urological Association* are [27]:

- Serum intact parathyroid hormone level should be obtained as part of the screening evaluation when primary hyperparathyroidism is suspected
- When a stone is available, a stone analysis should be obtained at least once
- Additional metabolic testing is recommended in high-risk or interested first-time stone formers and recurrent stone formers
- Metabolic testing should consist of one or two 24-h urine collections obtained on a random diet and analyzed at a minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium, and creatinine

20.2.5.2 Abdominal Ultrasound

Transabdominal Ultrasound

The gold standard for the diagnosis of urinary stones in nonpregnant patients is computed tomography. However, its application in

pregnant women is limited due to potential teratogenic effects of radiation. Therefore, the most appropriate first-choice diagnostic tool in pregnant women, despite its 60–78% sensitivity, is gray-scale ultrasonography [28, 29]. Ureteral stones might be difficult to demonstrate with ultrasonography given to their localization; in this case, assessing resistive index (RI) (>0.70) with Doppler increases the sensitivity up to 90% in order to display the presence of an obstruction (although the stone cannot be shown) [30, 31]. Although RI evaluation will not reveal the cause of obstruction, it is crucial in terms of showing the necessity of intervention.

Transvaginal Ultrasound

Transvaginal US might also be useful in distinguishing this physiological hydronephrosis, observed in 90% of the pregnant women, from ureter stones in the distal part of the ureter [21, 32].

20.2.5.3 Abdominal CT

In the nonpregnant state, unenhanced helical CT scan is the gold standard for diagnosing urinary calculi [33, 34]. Low-dose CT scan is more sensitive than renal ultrasound in locating urinary calculi during pregnancy [35]. The largest single radiation dose was 1.372 rads. This is down from an average dose of 2.2 rads [36].

20.2.5.4 MR Urography

If the accuracy of diagnosis is doubted, then MR urography can be used. It is comparable to CT and has the advantage of requiring safe and effective contrast media [37, 38]. Stones appear as storage defects and at the same time other causes that might lead to obstruction can be found, even outside the urinary system.

20.2.5.5 Intravenous Urography

Limited intravenous urography is useful to provide anatomic and functional information concerning the kidney [39]. Radiation exposure can be reduced if a limited sequence is employed and also by decreasing exposure times, low voltages, tight collimation, maximal fetal shielding, and prone patient positioning [39].

20.2.6 Treatment

20.2.6.1 Conservative Treatment

Medical management is most often successful (64–84%) with intravenous hydration and pain medications [36, 39, 40]. Ureteral stones become symptomatic mostly in the midtrimester, and this necessitates an intervention [18, 41]. In nonpregnant patients spontaneous passage is reported to be 68% in patients with <5 mm stone size and 47% in those with >5 mm stone size [42], whereas during pregnancy spontaneous passage rate is 70–80%, with some women experiencing spontaneous passage after delivery at a rate of 50% [39, 40, 43]. Spontaneous passage during pregnancy is higher partly due to physiologic ureteral dilatation. Because of the limitations in diagnostic methods, the rate of false-positive results is up to 23% [44]. Therefore it is argued that the high rate of spontaneous passage is based on misdiagnosis. In a conservative approach, patients must be attentively followed.

Diet Therapy

Diet therapy follow guidelines of *American Urological Association* for the general population [27]:

- The fluid intake that will achieve a urine volume of at least 2.5 l daily
- Limited sodium intake and consummation of 1–1.2 g per day of dietary calcium in patients with calcium stones and relatively high urinary calcium
- Limited intake of oxalate-rich foods and maintenance of normal calcium consumption in patients with calcium oxalate stones and relatively high urinary oxalate
- Increased intake of fruits and vegetables and limited nondairy animal proteins in patients with calcium stones and relatively low urinary citrate
- Limited intake of nondairy animal proteins in patients with uric acid stones or calcium stones and relatively high urinary uric acid
- Limited sodium and protein intake in patients with cystine stones

Pharmacologic Therapy

Diet therapy follow guidelines of *American Urological Association* for the general population [27]:

- Thiazide diuretics for patients with high or relatively high urine calcium and recurrent calcium stones
- Potassium citrate therapy for patients with recurrent calcium stones and low or relatively low urinary citrate
- Allopurinol for patients with recurrent calcium oxalate stones who have hyperuricosuria and normal urinary calcium
- Thiazide diuretics and/or potassium citrate for patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists
- Potassium citrate for patients with uric acid and cystine stones to raise urinary pH to an optimal level
- Allopurinol, but not as first-line therapy for patients with uric acid stones
- Cystine-binding thiol drugs, such as α-mercaptopropionylglycine (tiopronin), for patients with cystine stones who are unresponsive to dietary modifications and urinary alkalization or have large recurrent stone burdens
- Acetohydroxamic acid for patients with residual or recurrent struvite stones only after surgical options have been exhausted

Medical Expulsive Therapy

In addition to conservative treatment, spontaneous passage rate can be increased by medical expulsive therapy (MET) in these patients. As a part of MET, α-blockers and calcium channel blockers can be safely used during pregnancy [45].

Contraindications for MET and conservative treatment are [46]:

- Fever
- Infection
- Obstetric complications
- Solitary kidney
- Bilateral obstruction
- Intractable pain
- Oral intake problems
- Stones >1 cm

20.2.6.2 Surgical Treatment

Indications for surgical intervention are listed as contraindications for conservative treatment (see Sect. 20.2.6.1). The most commonly used procedures are percutaneous nephrostomy and placement of ureteral stents. Disadvantages of these temporary drainage methods emphasize the importance of definitive treatment.

Ureterorenoscopy with Lithotripsy

Ureterorenoscopy, which is a definitive treatment method, can be applied under spinal or general anesthesia and is a successful procedure. Outcomes are similar in general and pregnant population in terms of safety and efficiency [47].

Contraindications for ureterorenoscopy are [48, 49]:

- Infection
- Oversized stone
- Complex anatomy
- Bilateral obstruction
- Obstetric complications
- First trimester and near term

Ureteroscopy with holmium laser has become the procedure of choice in pregnancy for symptomatic stones less than 1 cm and in those without evidence of sepsis or history of transplanted kidney. The holmium laser has very limited penetration, 0.5–1.0 mm, making it well tolerated for surrounding tissue and has decreased sound intensity compared with the ultrasound, negating the possibility of fetal hearing damage [36].

Percutaneous Nephrostomy

Temporary drainage with percutaneous nephrostomy immediately decompresses the obstruction, can be done without ionizing radiation, can be performed on patients with acute sepsis, and requires quick and minimal anesthesia, but it also has many disadvantages. These include bleeding during insertion, dislodgement, the social aspect of dealing with the device, and necessity of multiple procedures because

encrustation of the catheter is accelerated requiring substitution every 4–6 weeks [39, 50, 51]. Percutaneous nephrostomy tube has a greater probability of infection and is more uncomfortable. If percutaneous nephrostomy has to be placed in an obstructed and infected system, a wide-spectrum antibiotic treatment (ampicillin–sulbactam) is mandatory; in other cases a prophylaxis with the first-generation cephalosporin is indicated [52, 53].

Ureteral Stents

Routine stenting after uncomplicated ureteroscopy in general population is not necessary. However, there is a subgroup of patients who probably benefit from stent placement, as evidenced by the higher hospital readmission rate. Pregnant patients should be included in this subgroup. The recommendation is to insert ureteral stents with pull-out strings to control early postoperative colicky pain and not to remove them sooner than 72 h. Ureteral stents may be placed but are associated with increased lower urinary tract symptoms, may cause damage to the ureter during placement, and ultimately may encrust over leading to obstruction. Classically, the decision to perform percutaneous nephrostomy versus stent placement is based on gestational age, with the former placed prior to 22 weeks and the latter afterward. The general opinion is that JJ stents would be more tolerated since it cannot be viewed outside the body by the patient; however, it is disadvantageous in terms of causing lower urinary system complaints.

During pregnancy, rapid calcification and encrustation of ureteral stents are pronounced, and 75% of patients were the ones whose stents were placed during pregnancy [54]. Asymptomatic bacteriuria, which can occur during pregnancy, can have a role in rapid stent encrustation especially with calcium phosphate and struvite stones. Also, hypercalciuria and hyperuricosuria that can be seen during pregnancy might be the reason for rapid encrustation. Therefore, it is suggested that stents should be changed every 4–6 weeks [50, 51, 55]. Comparative advantages of percutaneous nephrostomy and ureteral stenting are summarized in Table 20.2.

Table 20.2 Comparative advantages of percutaneous nephrostomy and ureteral stenting (reproduced from [11] under the CC BY 3.0)

Ureteral stenting	Percutaneous nephrostomy
Catheters cannot be observed outside the body	Catheters can be placed in different sizes (8–12 Fr)
Lesser risk of hemorrhage	Catheter can be irrigated
Interventional radiologist is not needed; any urologist can apply	Urine can be followed from the implanted kidney
No need for anesthesia	Ureteral complications can be avoided
	Placement can be made with local anesthesia

20.2.7 Prognosis

There is a 1.4–2.4-fold increased risk of premature membrane rupture and preterm labor in pregnant women with symptomatic nephrolithiasis [43, 56].

20.3 Acute Pyelonephritis

20.3.1 Incidence

Urinary tract infections (UTIs) are more common in women during pregnancy [57]. The incidence of asymptomatic bacteriuria is 2–7% in nonpregnant women and during pregnancy [57]. The two main types of UTI are cystitis and pyelonephritis. Acute pyelonephritis occurs in 1–2% of pregnancies [58, 59], and the condition is the second most common reason for hospitalization during pregnancy that is not related to delivery [60]. While still common in developing countries, during the past few decades, the incidence of acute pyelonephritis during pregnancy has decreased substantially in developed countries. Pyelonephritis in pregnancy occurs mostly before delivery, with all but 10–20% of cases diagnosed in the second and third trimesters [57, 61].

20.3.2 Etiopathogenesis

During pregnancy, anatomic and physiological changes occur in the urinary tract (see Sect. 20.1),

which increase the risk of developing a UTI. Also, asymptomatic bacteriuria increases the risk of developing acute pyelonephritis by 20- to 30-fold in pregnant women, compared to women without bacteriuria [57]. The trauma of delivery may induce bladder hypotonicity; frequent catheterization is often necessary and represents an additional risk factor. Among pregnant women with acute pyelonephritis, 9–17% were found to have concurrent bacteremia [59, 62, 63]. Notably, 3–5% of acute pyelonephritis cases are associated with diabetes mellitus [59, 64], a known predisposition for UTIs in general. Women with asymptomatic bacteriuria, defined as a urine culture from midstream collection with a single isolate of >100,000 colony-forming units of an uropathogen, are at increased risk of developing pyelonephritis in pregnancy compared to women without bacteriuria. Screening for and treatment of asymptomatic bacteriuria in pregnancy reduces the risk of subsequent pyelonephritis from approximately 20–35% to 1–4% [61]. Risk factors for acute pyelonephritis in pregnancy are summarized in Table 20.3. Despite increased adherence to guidelines recommending routine screening for asymptomatic bacteriuria in pregnancy, other age-related comorbidities may place the population at increased risk for pyelonephritis.

20.3.3 Clinical Presentation

Symptoms of acute pyelonephritis include fever, nausea, vomiting, or flank pain with or without the cystitis symptoms of painful, frequent, or urgent urination. Physical examination shows findings of fever and costovertebral angle tenderness. Isolated asymptomatic frequency (≥7 daytime voids) or nocturia is mostly physiologic. Physiologic frequency is reported by 59% in early pregnancy, 61% in mid-pregnancy, and 81% in late pregnancy [66].

The patient can present with septic shock. Acute pyelonephritis is the leading cause of septic shock during pregnancy [67].

Table 20.3 Risk factors for acute pyelonephritis in pregnancy [64, 65]

Urinary tract malformations
Low socioeconomic status
Asymptomatic bacteriuria
Hispanic or black
Less than 29 years
Diabetes mellitus
Multiparity

20.3.4 Differential Diagnosis

The difference in the sequence of events in acute appendicitis and acute pyelitis is important in differentiating them. In acute appendicitis, the findings are first pain, later fever, and rarely chills. In pyelitis chills come first, then fever, and pain (see Chap. 1).

20.3.5 Diagnosis

Repeated urinalyses usually confirm either bacteriuria or pyuria.

The utility of blood cultures in the management of acute pyelonephritis in pregnant women is not efficient. Only 1.3% of pregnant [68] and also 1.3% of nonpregnant female patients [63] had blood cultures with pathogens that differed from those found in the urine.

The most common associated diagnosis with acute pyelonephritis in pregnancy is anemia with the incidence of 22–25% [59, 64, 65].

20.3.6 Treatment

With the risk of severe complications from acute pyelonephritis during pregnancy, particularly in the latter half of the gestation, hospitalization was generally recommended for treatment and monitoring [69]. Recently, 0.5% of the pregnant women are hospitalized for acute pyelonephritis [65], which is less than previous reports [70]. Possibly the implementation of the guidelines for screening for asymptomatic bacteriuria in pregnancy by the *US Preventative Health Task Force* and the *American College of Obstetricians and*

Gynecologists may be partly responsible. It is also possible the high rates of early entry into prenatal care and the population characteristics might have contributed to the observed low rate. The average length of hospital stay is 2.8 days [64], which is comparable to previous reports (2.5 days) [70]. This presumably reflects the standard recommendation that a patient should be hospitalized with i.v. antibiotics until they remain afebrile for at least 24–48 h. There is no difference in length of stay between cases of pyelonephritis diagnosed in the first trimester versus the second and third trimesters [71].

> The severity of the acute pyelonephritis, not gestational age, determines the duration of hospitalization.

The most common pathogen among women with acute pyelonephritis in pregnancy is *E. coli* [59, 61, 72]. Treatment decisions to change initial antibiotic regimens were more affected by clinical course than by blood culture results (see Sect. 20.3.5).

20.3.7 Prognosis

20.3.7.1 Maternal Outcome

Nearly one-quarter of affected women will have ≥1 recurrences during the same pregnancy [73].

Maternal sepsis, renal failure, and respiratory insufficiency are among the associations found between pyelonephritis and maternal–fetal compromise [59]. Previous studies show 1–8% of cases had a concomitant diagnosis of respiratory insufficiency or adult respiratory distress syndrome [59, 64, 74]. The current study found 0.5% of ARDS due to acute pyelonephritis [65]. Contrary to previous reports [75], the most common uropathogen identified in women with ARDS and pyelonephritis was *E. coli*, not *K. pneumoniae* [65]. Severe lung disease or septic shock may be triggered by a cascade of proinflammatory cytokines, histamine, and bradykinins [76]. Diagnosis of sepsis/septicemia due to acute pyelonephritis was present in 12–17% of antepartum patients [59, 77].

The exact risk of preterm labor and delivery directly attributable to acute pyelonephritis in pregnancy is difficult to estimate, particularly because delivery may not occur during the admission for the acute disease, and the risk factors for both pyelonephritis and preterm delivery overlap [78]. Women with a diagnosis of acute pyelonephritis in pregnancy have a modestly higher (10.3% vs. 7.9%) [65] to significantly higher (5% vs. 1%) [59] likelihood of preterm delivery. Because most cases of pyelonephritis are encountered in the second and third trimesters, the threat of preterm delivery can result in tocolytic administration, which may compound the risk for pulmonary edema and respiratory insufficiency [75].

20.3.7.2 Fetal Outcome

Pregnant women with acute pyelonephritis are more likely to have premature delivery and a low birthweight infant [65, 79, 80]. However, pregnant women with asymptomatic bacteriuria seemed also to be more likely to have premature delivery and a low birthweight infant. Recommendations have been made to treat all pregnant women with asymptomatic bacteriuria [57, 81], although recently the relationship between asymptomatic bacteriuria and preterm delivery is not clear [65].

Urosepsis may be related to an increased incidence of cerebral palsy among preterm infants. It is not known whether urosepsis per se or infection or febrile state is the cause of cerebral palsy (see Chap. 23).

20.4 Acute Urinary Retention

20.4.1 Incidence

The risk of acute urinary retention (AUR) during pregnancy in Taiwan is 0.47% [82]. The incidence of AUR due to a retroverted uterus is 1.4% [83] or 1/3000 pregnancies [84]. AUR due to incarcerated retroverted uterus in the English literature up to 1995 was described in 27 cases [85]. Tumors of the lower urinary tract in pregnancy can also cause AUR. Fewer than 30 cases of bladder cancer during pregnancy have been described in the literature [86, 87], not a single one presenting as AUR.

20.4.2 Etiopathogenesis

20.4.2.1 Pregnancy

Retroverted Uterus

In the early pregnancy, the uterus is retroverted in 11–20% of women [83, 88]. As the uterus enlarges during the first trimester, the fundus normally rises from the hollow of the sacrum to an anterior ventral position, spontaneously correcting any retroversion before 14 weeks of gestation. In rare cases, when uterus fails to ascend into the abdominal cavity, the fundus becomes wedged below the sacral promontory, where it continues to enlarge [84]. Concomitantly, the cervix becomes displaced cephalad against or above the symphysis pubis causing compression of the urethra and bladder neck [89], which interferes with normal voiding (Fig. 20.4). During the day, irritation of the bladder leads to dysuria, the frequency of urination preventing bladder distention. When the patient waits too long before urinating, urine accumulates in the lower part of the bladder creating differences in pressure between the bladder and the urethra, which permit spontaneous urination, protecting the bladder against distention. In contrast, when the patient is in the supine position, the upper part of the bladder becomes dependent on bladder filling for urination, and the differences in pressure between the bladder and the urethra are greatly diminished, favoring the accumulation of urine in the bladder without any need for emptying. This anatomic change further disturbs the pressure ratio allowing spontaneous bladder emptying and thus leads to AUR. This phenomenon explains the higher frequency of AUR during the night or when the patient first awakens in the morning [90].

Conditions that may inhibit the fundus of the enlarging uterus from ascending out of the sacral hollow include adhesions related to previous pelvic surgery, pelvic inflammatory disease, or endometriosis; large fibroids; uterine malformation; or a deep sacral concavity with an overhanging promontory and/or laxity of the supporting tissues [91, 92]. Incarceration can also occur in the absence of predisposing factors [93, 94]. Why so few patients develop this complication is not clear, but AUR can result from other factors in addition to the retroverted uterus. In addition to AUR, other complications can be (simultaneously) present. There is almost double the incidence of spontaneous abortion in early pregnancy in patients with the retroverted uterus [83].

Tumors of the Bladder

Most incident bladder cancers affecting women occur in those aged older than 55 years with a mean age at diagnosis of 71 years. However,

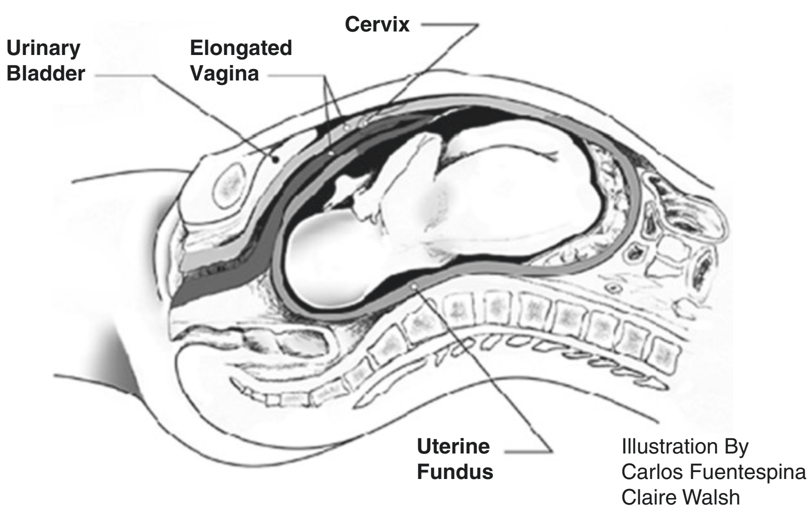

Fig. 20.4 Illustration of an incarcerated uterus at term. Notice the elongated vagina with the uterine fundus and the fetal head impacted deep in the pelvis. Reproduced with permission from [95]

about 1% of tumors of the bladder are found in women in the first four decades of life [96]. These rare reports of bladder cancers occurring in the younger pregnant population [97] are associated with cigarette smoking and higher stage at diagnosis [98].

Uterine Fibroids

The presence of a posterior intramural fibroid favors retroversion which is exaggerated in pregnancy due to the increasing vascularization of the uterus accompanied by the growth of any fibroid. Consequently, if the fibroid is located in a posterior and lower or isthmic position, it can promote incarceration of the uterus or can itself become incarcerated in the pelvic cavity [90].

20.4.2.2 Postpartum

Postpartum AUR has no standard definition. In 2001, Calgary Health Region's policy and procedures outlined postpartum AUR as the catheterization of the bladder within the first 24 h postpartum for not voiding within 6 h postpartum, to micturate often in small amounts or to have an urge to micturate but cannot or to be catheterized for any reason for an amount of 500 mL output within the first 24 h postpartum [99]. In 2002, *International Continence Society* defined the condition as the presence of painful, palpable, or percussive bladder in a patient who is unable to pass any urine [100].

20.4.3 Clinical Presentation

20.4.3.1 Medical History

Retroverted uterus itself causes nonspecific and general urinary symptoms like dysuria, overflow urinary incontinence, urinary frequency (more common in exaggerated uterine anteflexion due to pressure on the bladder), and urinary infection in early pregnancy. The symptoms are due to the pressure of retroverted uterus to the adjacent pelvic organs also causing tenesmus, abdominal pain, and swelling of the lower extremities as a result of compression of the common iliac veins [84]. Vaginal spotting or frank bleeding in the early stages of pregnancy is also common [83]. However, if retroverted uterus remains undiagnosed and pregnancy advances, it can cause severe obstetric and nonobstetric complications including AUR [101]. Usually, AUR due to retroverted uterus occurs before 20 weeks of gestation.

In general population, in 75% of cases, the initial symptom of urinary bladder carcinomas is painless, intermittent, and often terminal hematuria. The other 25% of cases have various related symptoms such as painful urination and frequency [102, 103]. These symptoms may suggest cystitis.

20.4.3.2 Physical Examination

Pelvic examination reveals a (severely) retroflexed uterus with an anterior cervix and superiorly displaced urinary bladder. The cul-de-sac is filled with the softly enlarged uterus bulging into the vagina. Uterine myomas, being the cause of AUR or not, can be palpated [90].

20.4.4 Differential Diagnosis

Delay in the diagnosis of uterine incarceration can lead to other complications that can even mask AUR. These include fetal loss (up to 33%), infection, uterine rupture, vascular obstruction, ureteral obstruction, bladder ischemia, bladder rupture, or rectal gangrene. Other complications during the pregnancy may include preterm labor, intrauterine growth restriction, labor dystocias, and difficulty with hysterotomy at the time of CS [84, 104, 105]. Underlying causes of AUR in pregnancy are summarized in Table 20.4.

Table 20.4 Causes of acute urinary retention during pregnancy

Retroverted uterus
Uterine myoma (± retroverted uterus)
Bladder tumor
Threatened miscarriage
Placenta previa
Shock (all cause)

20.4.5 Diagnosis

20.4.5.1 Laboratory Findings

When a pregnant woman presents with symptoms of UTI with negative urine culture, a pelvic examination should be done, and retroverted uterus compressing urethra should be kept in mind. If AUR due to the retroverted uterus is detected, postvoidal urine volume should be controlled which will also resolve the patient symptoms [106].

20.4.5.2 Transvaginal Ultrasound

First imaging method for defining the bladder status and delineating the cause of AUR is a transvaginal ultrasound. It can show retroverted uterus (Fig. 20.5) or uterine fibroid causing either retroversion or direct urinary bladder compression.

20.4.5.3 Abdominal MR

Abdominal MR is the best imaging modality for both the diagnosis of the incarcerated uterus and the morphology of the fetus (Fig. 20.6).

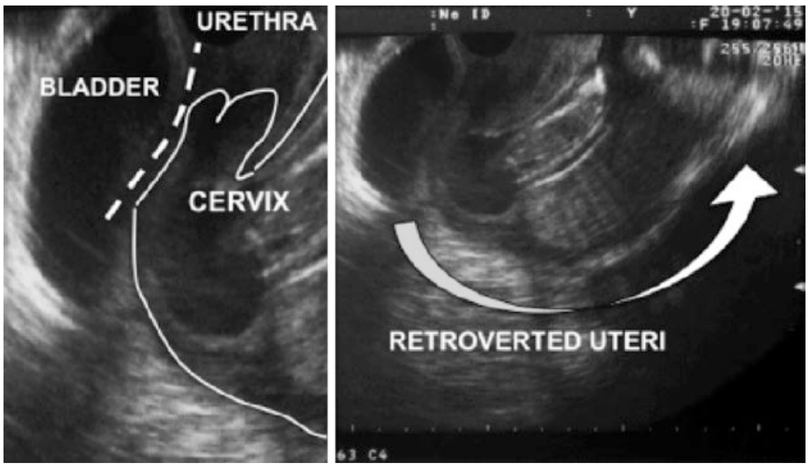

Fig. 20.5 Transvaginal ultrasonography showing a retroverted uterus during pregnancy. The cervix lies posteriorly to the urinary bladder, and the uterus normally extends superiorly from it, but the direction of the body of the fetus reveals that the uterus extends backward (reproduced from [107])

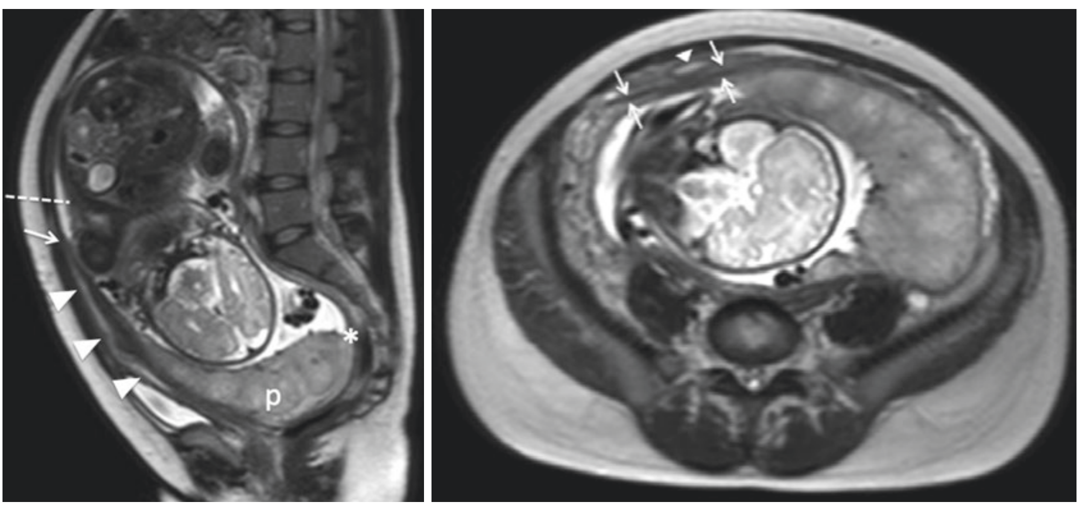

Fig. 20.6 Abdominal MR of incarcerated uterus at 34 weeks of gestation. (*Left*) sagittal view, T2-weighted, showing extremely elongated cervix (*arrowhead*). The incarceration of the uterus (*asterisk*), including the fetal head and placenta (*p*), in the pouch of Douglas. This view shows the placenta placed in the posterior wall of the uterus and has sufficient margins from the internal cervical os (*arrow*). The level of the hysterotomy is indicated by the dotted line (…), located above the internal os to avoid cervix and posterior uterine wall injuries. (*Right*) low T2 signal intensity (*arrows*) behind the cervix showing the space between the cervix and posterior uterine wall in the axial view (reproduced from [108] under the CC BY 4.0)

20.4.5.4 Cystoscopy

> A thorough investigation of the lower urinary tract is mandatory, including cystoscopy, in pregnant patients with a retroverted uterus, who develop acute urinary retention [109].

There are cases of concomitant bladder pathology, including bladder cancer in a patient with AUR due to the retroverted uterus [109].

20.4.6 Treatment

An early diagnosis is important for successful treatment because the reduction of the uterus is more likely in the early pregnancy and late complications like bladder atony, postobstructive diuresis, renal failure, and bladder rupture can be seen if AUR due to retroverted and incarcerated uterus is undiagnosed [84, 106, 110].

Yang and Huang proposed the following simple preventive measures [111]:

- Restriction of liquid intake in the evening, before going to bed
- Urination before going to bed and preventive urination during the night
- Credé's maneuver, consisting of leaning forward in a sitting position at the beginning of urination
- Moving from a supine to a prone position before getting up
- Avoidance of Valsalva maneuver

20.4.6.1 Manual Reduction

Empty bladder (urinary catheter if necessary) and bowel are important before the procedure [112]. If the procedure is performed on the awake patient, then the patient is given 10 mg morphine sulfate intramuscularly and placed in the knee–chest position. The incarcerated uterus is gently reduced (see next paragraph). In the awake patient, the maneuver of manual uterine reduction results in immediate relief of the tenesmus and bladder discomfort.

If this fails, frequent knee–chest exercises and daily attempts of manual reduction are performed.

If these fail, general (mostly in advanced pregnancy) endotracheal anesthesia with propofol induction and succinylcholine for maximum uterine and patient relaxation is done [112]. It is advisable to perform this maneuver under sonographic guidance [112, 113]. The operator's hand is placed in the vagina in the posterior fornix. With gentle pressure cephalad on the uterine fundus while using ultrasonography, the fetal head is displaced from under the symphysis cephalic to the pelvic brim. Ultrasonography assesses the position of the fetus and confirms the uterine fundal release. Repeated vaginal examination confirms the absence of the previously palpated uterine mass. Continued pressure applied by the vaginal hand and one hand placed on the abdomen over the fetal head guides the fetus into a cephalic presentation. Gentle but continuous cervical traction can be applied (Fig. 20.7). Ultrasonography reveals the location of the placenta, the cervix, and the fundus in its normal positions. The Foley catheter is left in place and the patient kept on bed rest for 24 hours. Final ultrasonography is done prior to hospital discharge.

If manual reduction fails, colonoscopic insufflation of sigmoid colon to facilitate the manual repositioning of the uterus is an option [104]. A loop is formed routinely when advancing the endoscope through the sigmoid colon [104]. In this specific situation, the air insufflation during the procedure together with the formation of the loop has a synergistic effect by creating anterior pressure through the wall of the rectum on the uterine fundus (Fig. 20.8). The ability of the

Fig. 20.7 The technique of manual uterine replacement with the patient in the knee–chest position. Reproduced with permission from [114]

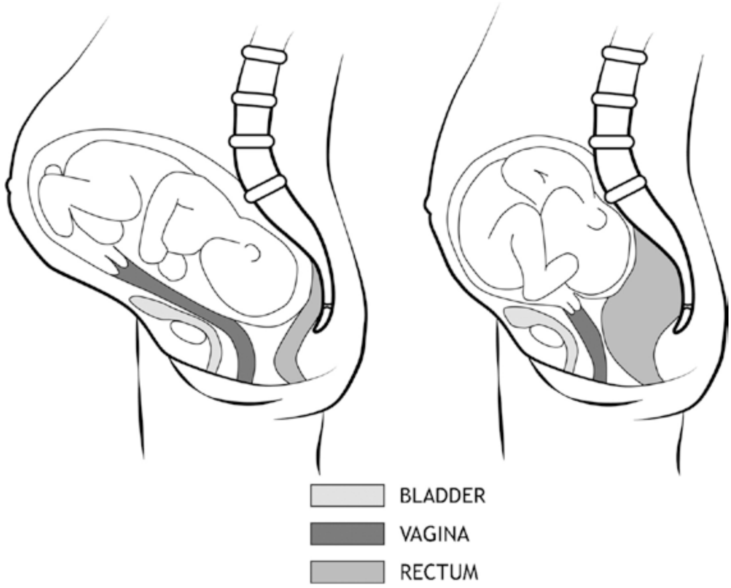

Fig. 20.8 Colonoscopy-assisted repositioning of the incarcerated uterus. The ability of the colonoscope to get above the uterine fundus, together with the extra anterior pressure provided by the loop formation and air insufflation, makes the rate of success of this procedure quite higher than the manual maneuvers. Reproduced with permission from [115]

colonoscope to create an air cushion underneath the incarcerated uterus makes the success rate of this procedure higher than that manual maneuvers.

Once reduced, a uterus large enough to become impacted usually will remain an abdominal organ with no additional support, though a pessary occasionally may be needed. A postobstructive diuresis may occur following reduction of the incarcerated gravid uterus [110].

20.4.6.2 Surgical Reduction

If after 3–4 days of conservative measures no reduction is accomplished, operative reductions may be required [116]. More invasive treatment modalities like reduction with laparoscopy or laparotomy could be performed, but these interventions carry the risk of maternal and fetal morbidities [92, 117].

20.4.6.3 Obstetric Management

Increased bleeding is expected due to easier passage of uterine contents after manual reduction of incarcerated uterus [116]. Bleeding mandates subsequent suction and curettage [116].

Prevention and Treatment of Preterm Labor

See Chap. 23.

20.4.7 Prognosis

> AUR due to the retroverted gravid uterus is a risk factor for the recurrence of AUR during the next pregnancies [111, 118].

The possibility recurrence of AUR should be explained to these patients and the necessity of preventive measures for minimizing the possibility of AUR during the first trimester of their next pregnancies (see Sect. 20.4.6). The reasons for recurrence are not clear, because mostly, except for retroversion of the uterus contributing to AUR, there are no other abnormalities [111, 118].

20.5 Renal Collecting System or Parenchymal Rupture

20.5.1 Incidence and Etiopathogenesis

20.5.1.1 Spontaneous Rupture

There are three classic mechanisms of spontaneous renal rupture in pregnancy [119]:

- Spontaneous rupture with no cause
- Rupture of the excretory tract related to an obstruction

- Renal rupture secondary to a tumor (mostly angiomyolipoma)

Between 1947 and 1995 there were 25 published cases of rupture of the urinary tract during pregnancy with 12 patients with ruptures of the collecting system and 13 with ruptures of the renal parenchyma [120]. In 2010, 18 cases of spontaneous renal rupture during pregnancy were collected, 13 of which occurred in patients with normal kidneys (no underlying explanation for ruptures such as infection, abscess, stone, or tumor). Almost all (12/13) cases of rupture occurred on the right side, likely owing to the fact that hydronephrosis is more common and severe on the right side due to uterine dextroversion [121, 122]. Up to 2015, there were 37 published cases of spontaneous urinary tract rupture during pregnancy, 13 of which occurred on the left side [123, 124]. Although calyceal rupture can occur in kidneys with or without preexisting pathology, a significant proportion of spontaneous upper urinary tract or kidney ruptures during pregnancy is associated with renal calculi [122, 123]. Nineteen (plus one without proven but with previous urolithiasis) of the thirty-seven cases occurred in patients with some form of underlying kidney pathology such as infection, abscess, stones, or tumors, either in the past or at the time of rupture [123, 124].

The increase in size and changes in the structure of the parenchyma make the lesions more susceptible to minor trauma from either external or internal sources [125].

Upper Urinary Tract Obstruction

During pregnancy, the renal pelvis and ureter dilate. Hydronephrosis may develop from the 6th to 10th week of gestation [126], and according to Gillenwater, rupture of the collecting system can occur from week 18 of gestation up to day 1 post-delivery [127]. In order to progress to rupture, the hydrostatic pressure needs to exceed the holding capacity of the calyceal–renal capsular junction [127] and the protective mechanism of spontaneous extravasation of the urine through the calyceal fornices. The increased pressure within the pelvicalyceal system generates stretching and decreased the elasticity of the capsule and soft tissue attenuation [126]. There is a higher probability for a rupture to take place in an area where the normal structure was altered by infections, tumors, or scarring [128].

A sudden increase in intrapelvic pressure may result in spontaneous extravasation of urine through the calyceal fornices. This is a physiological protective phenomenon and is seen in excretory urography performed with external compression and will result in pyelotubular, pyelosinus, and pyelolymphatic backflow. This extravasation resolves spontaneously and without sequelae [129]. A true rupture of the renal pelvis is, however, quite different and results in urine extravasation into retroperitoneal space. Urine and blood can dissect along fascial planes to produce an extensive retroperitoneal urinoma, hematoma, or later abscess. These dissections may break through the peritoneal covering and produce chemical or infective peritonitis. Most reported cases of nontraumatic rupture of a normal kidney were due to pelvic or calyceal rupture [130].

The occurrence of hydronephrosis secondary to pregnancy has been a well-recognized condition even in 1905 [131] by Erich Carl Otto Opitz (Fig. 20.9). The right ureter is affected more often than the left because the right ureter crosses the iliac artery proximal to the pelvic brim and tends to lie on the less rigid vein with less tendency toward being compressed [132]. Abnormal ureteral peristalsis has not been consistently found [133]. Therefore, the pregnancy-related obstruction can be due to [134]:

- Incarcerated gravid uterus
- Chronic ectopic pregnancy
- Polyhydramnios
- Normal pregnancy

True Spontaneous Rupture

Spontaneous rupture with no underlying condition is a phenomenon observed more frequently on the right side [120, 130, 135–137]. Stadfeldt reported right hydroureteronephrosis caused by uterine compression of the ureter at the level

of the iliac vessels in 1861 [138]. Possible explanations coupled with the hormonal ureteral atony [139] are:

- Compression of the right ureter caused by the physiological dextrorotation of the gravid uterus
- Engorged right ovarian artery or vein

Renal Angiomyolipoma Rupture

The angiomyolipoma (AML) is often a benign tumor consisting of three types of histologic features: adipocytes, smooth muscle cells, and blood vessels with thickened wall. The incidence of renal AML is 0.3% in the general population and represents 3% of solid renal masses, being even more infrequent during pregnancy [140, 141]. The risk of spontaneous rupture associated with pregnancy is higher [142, 143].

20.5.1.2 Traumatic

Traumatic renal rupture is most commonly seen after motor vehicle accidents [144, 145]. One of the first reports was by Gemmill and Martin (New York) in 1933 [144].

Fig. 20.9 Erich Carl Otto Opitz (born 1871 in Breslau, died 1926 in Garmisch) was German gynecologist. He was editor of the journal *Deutsche Frauenheilkunde* (Reproduced from Wikipedia)

20.5.2 Clinical Presentation

20.5.2.1 Medical History

The initial clinical manifestations of pyeloureteral leakage may range from mild flank discomfort to unremitting pain associated with an acute abdomen when rupture occurs. Such pain is due to urine or blood dissecting along the fascial planes with or without disrupting the peritoneal covering to produce an infective or chemical peritonitis [125]. Sometimes the pain may be associated with pyrexia, suggesting an infected urinoma, abscess, or chemical peritonitis. Therefore, renal rupture during pregnancy can be confused with other causes of acute abdomen. Sometimes patients complain of suprapubic pain which depends on the level of obstruction. Additionally, the patient can present with nausea and vomiting. A history of a remote UTI and/or history of urolithiasis prior to current pregnancy can be elicited [124]. Even anuria can be presenting symptom caused by complete obstruction of the ureters by the gravid uterus [134].

20.5.2.2 Physical Examination

On examination, the patient is alert and oriented, not pale or cyanotic, but is anxious, restless, and complaining of severe pain in the more advanced presentation. Signs on physical examination depend on the cause of renal/collecting system rupture and the level of obstruction if the cause. Percussion flank tenderness is always present. If the obstruction is at the level of vesicoureteric junction or distally, abdominal or suprapubic tenderness is also present. Peritoneal signs are almost always absent. This presentation may be associated with pyrexia, suggesting an infected urinoma, abscess, or chemical peritonitis. Mild tachycardia is common [123]. With a parenchymal tear, a palpable mass is generated by the leaking urine, and blood can be felt on examination of the flank [126].

Parenchymal ruptures are associated with sudden hematuria, loin pain, loin mass, and or hypotension, while a calyceal rupture usually presents with loin pain with or without hematuria [120] but without hypotension.

Traumatic renal injury/rupture is rarely an isolated injury with maternal blunt abdominal trauma. Therefore, other intra-abdominal injuries should be sought (see Chap. 10).

20.5.3 Differential Diagnosis

Flank pain during pregnancy is a common complaint with a broad differential diagnosis (Table 20.5).

20.5.4 Diagnosis

The diagnosis of renal rupture during pregnancy is often one of exclusion.

20.5.4.1 Laboratory Findings

Urinalysis can reveal UTI or more pronounced bleeding due to urinary tract calculi, while urine culture sometimes does not confirm bacterial growth [124]. Leukocytosis is always present. BUN and creatinine depend on the preexisting renal status and the cause of renal/collecting system rupture. If the obstruction was the cause, these values will be above normal limits. Urinalysis can reveal micro- or macrohematuria. Gross or microscopic hematuria is more common with parenchymal rupture than rupture of the collecting system [130]. Nitrites and leukocytes in the urine are indicative of UTI [123]. Liver function tests, amylase, and lipase should be obtained to rule out the acute liver, biliary, and pancreatic causes of acute abdominal pain.

20.5.4.2 Transabdominal Ultrasound

Serial ultrasound with duplex Doppler studies plays an important role in the detection of the ruptured kidney for those patients with symptomatic hydronephrosis [135]. If there is a high degree of suspicion, serial ultrasound should be performed regularly especially when there is a symptomatic presentation with minimal benign appearing perinephric collection on initial ultrasound [126]. There is a proposed method [148] ultrasound differentiation between physiological and pathological dilatation of the renal collecting system in pregnant patients (Fig. 20.10), based on the extension of the dilated ureter in relation to the common iliac artery – a physiological hydronephrosis will extend down only to the level of the artery while in a pathologic obstruction it will extend below the artery.

20.5.4.3 Abdominal CT

The preferred imaging study for renal trauma in general population is intravenous-enhanced CT [149, 150]. It provides the most definitive staging information: parenchymal lacerations are clearly defined; extravasation of contrast-enhanced urine can be easily detected (Fig. 20.11); associated

Table 20.5 Differential diagnosis of flank pain in pregnancy depending on the presence of blood loss [124, 146, 147]

No blood loss	Blood loss
Acute hydronephrosis	Liver/spleen trauma
Nephrolithiasis/urolithiasis	Liver/spleen rupture
Acute pyelonephritis	Heterotopic/ectopic pregnancy
Renal cysts	Uterine rupture
Renal malignancy	Placental abruption
Constipation	Renal angiomyolipoma
Gastrointestinal infections	
Acute appendicitis	
Acute cholecystitis	
Acute pancreatitis	
Ovarian cysts/tumors	
Uterine fibroids	
Pelvic inflammatory disease	
Musculoskeletal pain/trauma	
Cystitis	

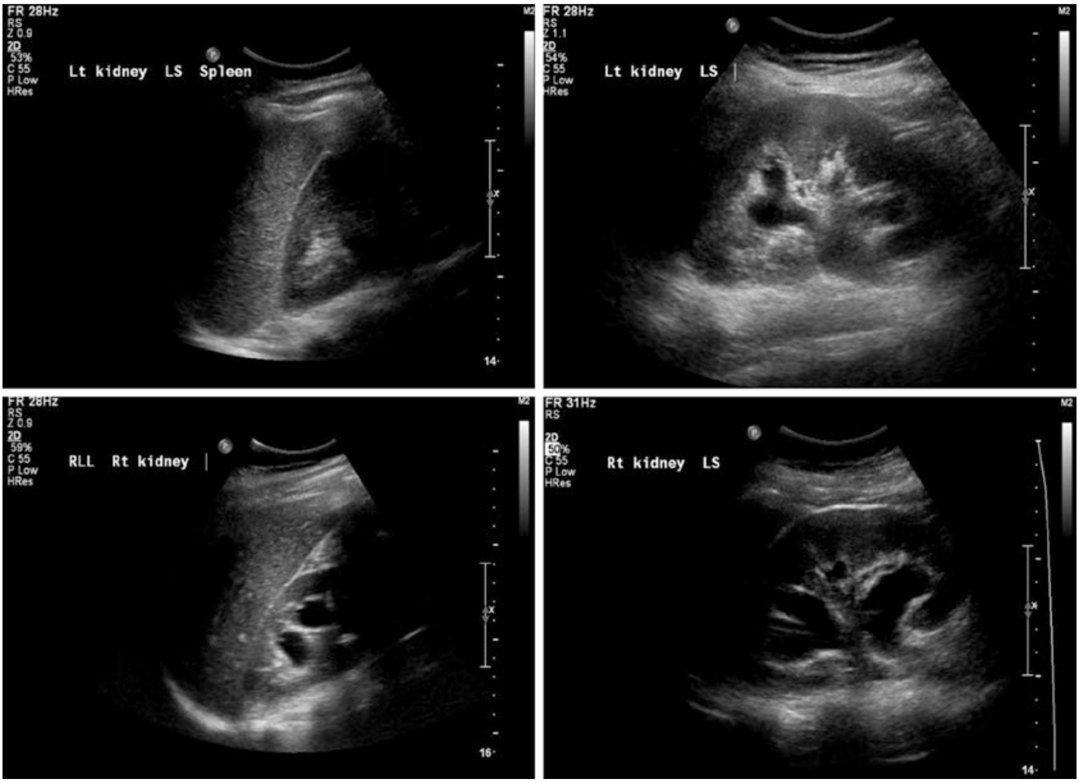

Fig. 20.10 Renal ultrasound revealed bilateral dilatation of the renal collecting system (deemed physiological), predominantly on the right, with no sonographic evidence of renal calculi (reproduced from [123] under the CC Attribution License)

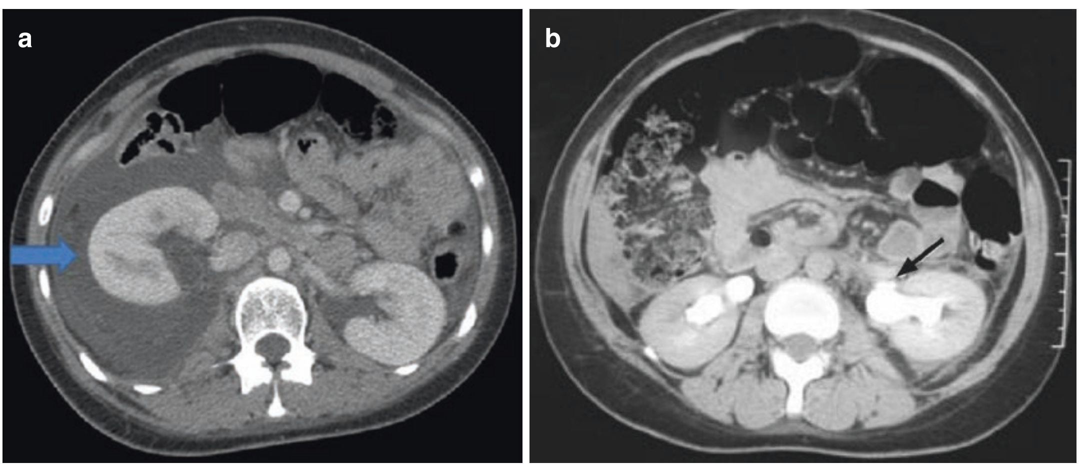

Fig. 20.11 (**a**) Abdominal CT without contrast without evidence of nephrolithiasis but reveals urinoma (*blue arrow*) (reproduced from [151] under the CC Attribution License). (**b**) The excretory phase of CT of the postpartum patient showing extravasation of contrast (*black arrow*) from the left renal collecting system. Reproduced with permission from [122]

injuries to bowel, pancreas, liver, spleen, and other organs can be identified; and the degree of retroperitoneal bleeding can be assessed. If the abdominal CT is done without contrast, urinoma can be found and differentiated from hematoma according to the Hounsfield units (Fig. 20.11).

20.5.4.4 Abdominal MR/MR Urography

If transabdominal ultrasound does not reveal the cause of patients' symptoms or ultrasound findings do not correlate with clinical presentation, abdominal MR is recommended. MR can delineate perinephric fluid and retroperitoneal fluid consistent with calyceal rupture and urine leak (Fig. 20.12). Urinary tract stones are visualized if present [124]. This imaging method replaced excretory urography due to its ionizing radiation. It can allow urinoma to be distinguished from hematoma because of the characteristic high-intensity signals of acute hematoma on the T1-weighted images [135]. In addition, MR urography delineates adjacent parenchymal structures and can define underlying pathology.

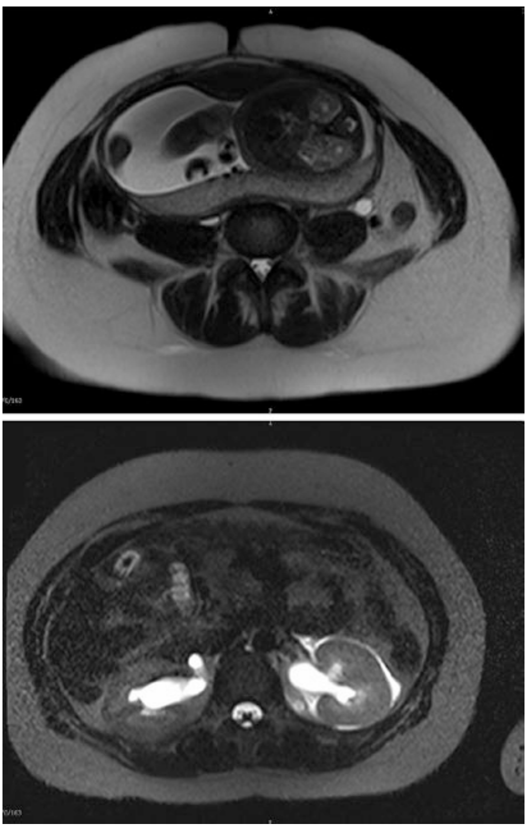

Fig. 20.12 An MR urogram demonstrated mild bilateral hydronephrosis and proximal hydroureter, with compression of the distal ureters by the gravid uterus. Perinephric fluid was identified considered related to pelvicalyceal rupture, on the left, with no evidence of calculi (reproduced from [123] under the CC Attribution License)

20.5.4.5 Excretory Urography

Before the widespread use of abdominal CT and MRI, limited excretory urography (intravenous pyelography) was used for delineation of the urinary excretory tract. An i.v. urogram with only two films (<1 rad) can be helpful in identifying the site of rupture without associated harm to the fetus [152]. Dilation of urinary tract system or extravasated contrast material from the renal pelvis could be found (Fig. 20.13). Urinary tract calculi can be visualized depending on the radiolucency. It is also useful in determining the site and the nature of the rupture or obstruction, the amount of extravasation, and the function of the kidneys (Fig. 20.14).

20.5.5 Treatment

There is no consensus or evidence-based options of treatment for spontaneous urinary tract rupture in pregnancy. The treatment method may depend on the rupture site and severity [122] and on the clinical situation: rupture of a septic urinary system and rupture of the renal parenchyma. The goals of treatment are to preserve renal function,

Fig. 20.13 Limited excretory urogram in 34-week pregnancy, showing extravasation of contrast material in the lower pole of the right kidney (*arrow*). Fetal skeleton is visible. Reproduced with permission from [125]

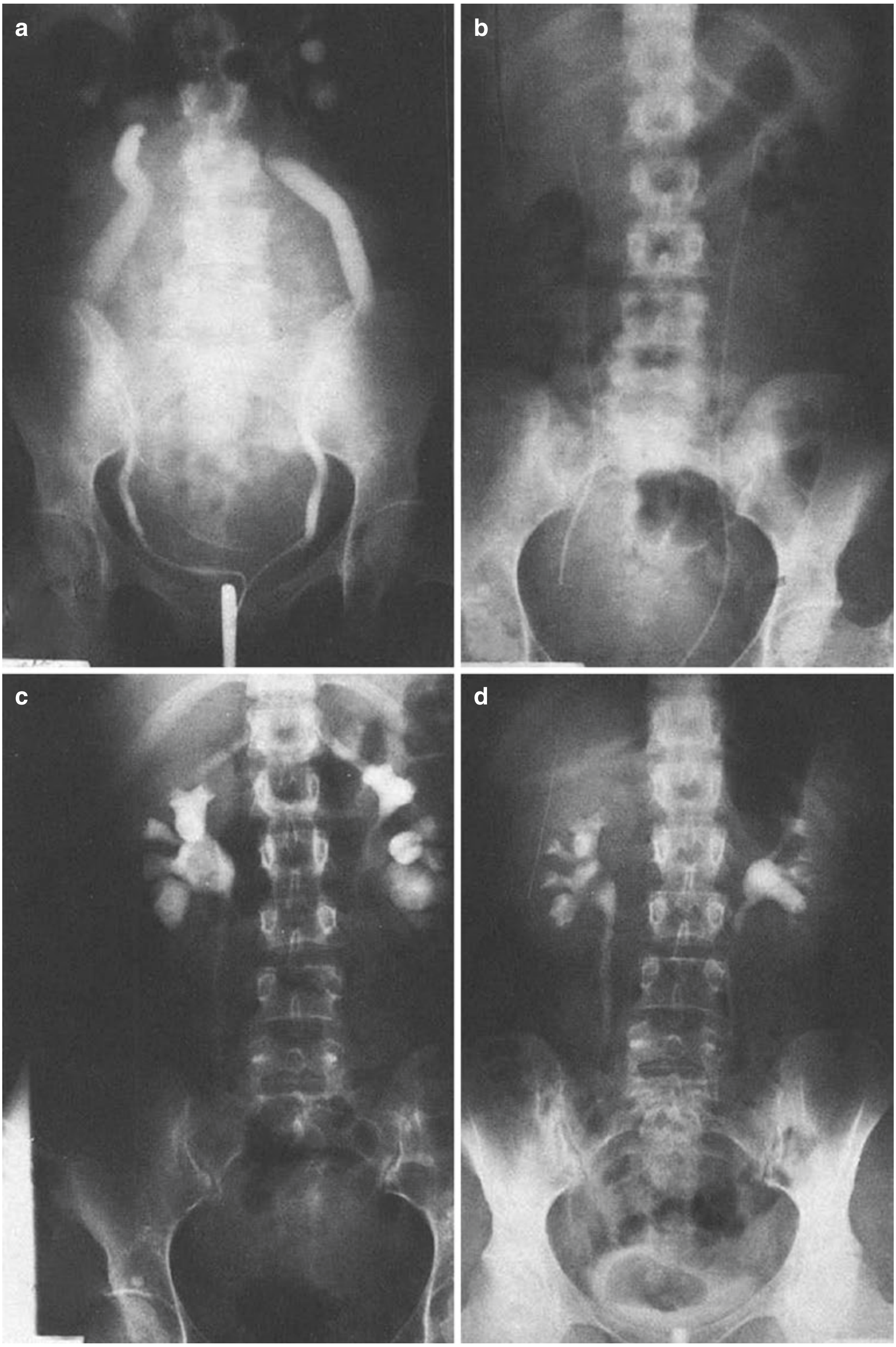

Fig. 20.14 (**a**) Initial placement of ureteral catheters under local anesthesia. (**b**) Ureteral stents in place. Intravenous urograms (**c**) day after stent removal and 3 weeks after full-term delivery and (**d**) 8 weeks after scent removal. Reproduced with permission from [134]

relieve pain, allow the site of rupture to heal spontaneously [153], and promote the safe progress of the pregnancy to full term and safe delivery with minimal disturbance for the baby [123].

20.5.5.1 Conservative Treatment

When patient's clinical improvement prior to any invasive intervention is obvious, there is no indication for surgical intervention. Conservative management may be applied to small perinephric collections [126]. Analgesia is titrated according to the patients' requirements, and leukocyte, BUN and creatinine levels, and urinalysis are checked regularly to detect disease progression. Antibiotics are administered if urinalysis or urine culture shows positive results.

Hydronephrosis of pregnancy is almost always a benign condition, and relief of renal colic from acute obstruction may be obtained by a positional change to left lateral or knee–chest position [154]. Retroverted or incarcerated uterus rarely causes upper urinary tract obstruction; it causes bladder obstruction (see Sect. 20.3.5).

20.5.5.2 Surgical Treatment

Ureteral Stents

A JJ stent is probably the least invasive effective method for controlling pain and progression of the rupture and also allowing the pregnancy to progress to full term. The advantages of a JJ stent are pain relief and free drainage, facilitating the closure of the communication between the pelvicalyceal system and perinephric space [126]. Stents are also indicated when gravid uterus compression is the cause of severe bilateral hydroureteronephrosis (Fig. 20.14). If a documented obstructive cause such as a persistent large renal stone following calyceal rupture, more aggressive intervention such as ureteroscopic lithotripsy combined with ureteral stenting is indicated. Appropriate antibiotic coverage and close follow-up are important.

Percutaneous Nephrostomy

While analgesia and conservative therapy are appropriate forms of initial management for patients with symptomatic obstruction, patients with pain that persists despite analgesia should receive surgical intervention with percutaneous nephrostomy or ureteral stenting [56, 122]. Percutaneous nephrostomy (Fig. 20.15) is indicated when retrograde

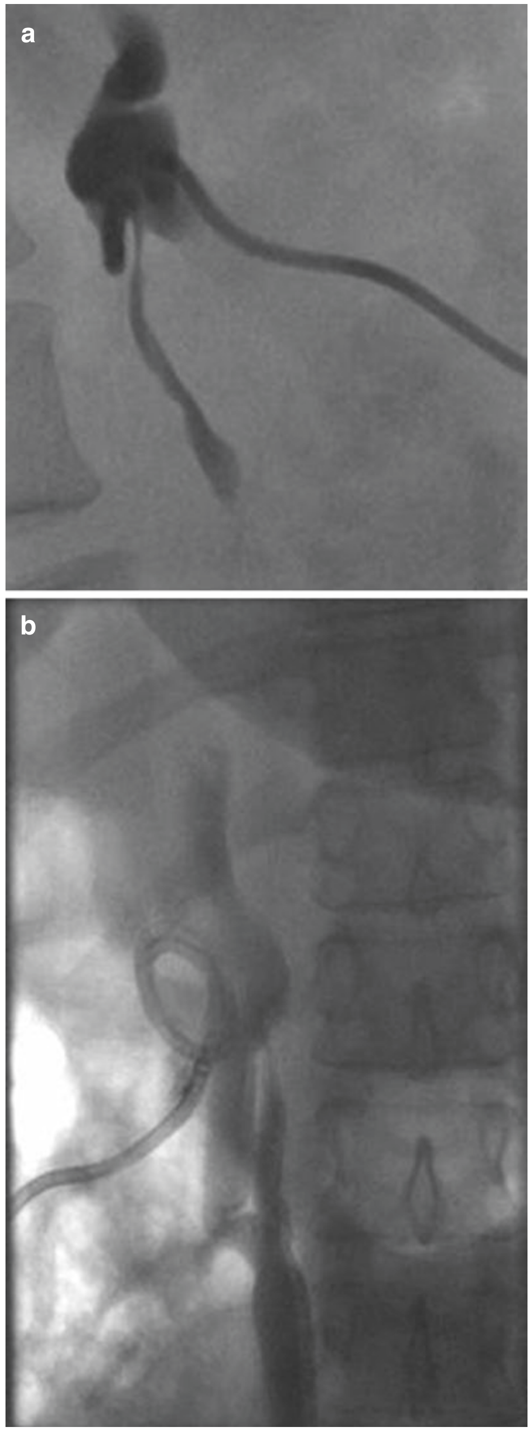

Fig. 20.15 (**a**) Initial placement of ureteral catheters and (**b**) catheter in place during remaining pregnancy (reproduced from [123] under the CC Attribution License)

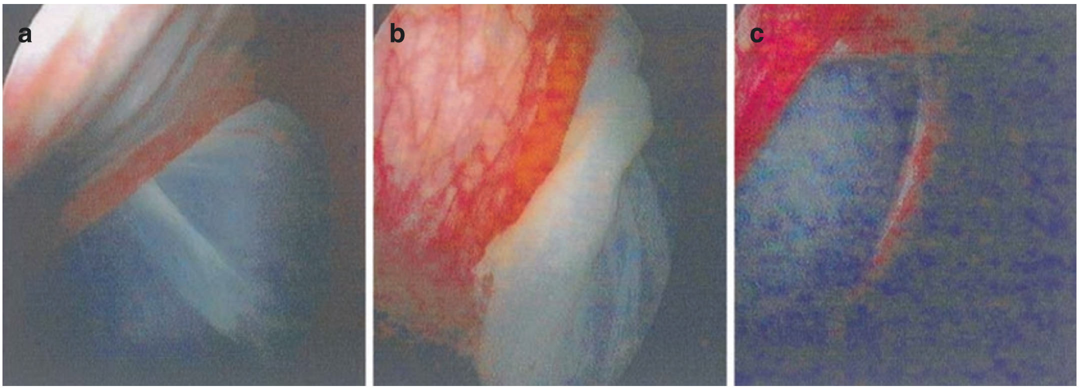

Fig. 20.16 (**a**) Cystoscopic view: herniation of amniotic sac in the bladder. Evidence of a whitish, roundish neoformation with a perfectly smooth surface protruding in the bladder; (**b**) gradual reduction of the herniation of the amniotic sac during bladder filling; (**c**) the complete disappearance of the herniation showed the oval vesical tear of the hernial neck. Reproduced with permission from [180]

ureteric stenting fails because of the tortuosity of the dilated ureter [122]. Sometimes, after (induced) labor symptoms resolve spontaneously before surgical intervention [124].

Exploration
Exploration is indicated when (bilateral) ureteral obstruction cannot be relieved and the compressing mass should be removed [155]. Another indication is the associated hemorrhage. In all previously reported cases, the treatment was nephrectomy [125]; however, a more conservative approach (partial nephrectomy) may be possible in selected cases [156]. It is important to know the status of the other kidney before operating on one kidney.

20.5.5.3 Obstetric Management
In pregnancies complicated by polyhydramnios, the renal failure is caused by ureteral obstruction secondary to compression by the massively enlarged uterus. Attempts at amniocentesis are usually unsuccessful, and induction of labor by amniotomy is the treatment of choice [157].

20.5.6 Prognosis

Imaging is often not helpful until rupture has occurred, a definitive cause of obstruction is often not found, and once the rupture has occurred, recovery is often uneventful. The natural course of this disease, however, is the resolution of symptoms following rupture as long as no secondary infection develops. Further, there are no clear guidelines regarding how to manage this type of patient in the puerperium and how to counsel patients in subsequent pregnancies.

Renal failure caused by obstruction does not occur in pregnant patients who have ectopic or pelvic kidneys although there is an increased incidence of Cesarean section (CS) because of difficult labor.

20.6 Urinary Bladder Injury/Rupture

Urinary bladder injury or rupture is very infrequent in pregnancy and puerperium. Even current guidelines and consensus statements of *European Association of Urology* [158] and *Société Internationale d'Urologie* [159] do not discuss bladder injuries in pregnancy.

20.6.1 Incidence

The incidence of bladder injury during CS ranges 0.0016–0.94% [160–164] with an increase in situations where previous abdominal surgery, previous CS, prolonged second stage of labor, and

Cesarean hysterectomy have occurred [161]. The incidence does not appear to have changed in the last half of the century. The dome of the bladder is the site most frequently injured.

20.6.2 Etiopathogenesis

Intraperitoneal bladder rupture causes urinary peritonitis (uroperitoneum).

20.6.2.1 Spontaneous Bladder Rupture

In general population, spontaneous bladder rupture is usually associated with recent trauma, malignancies, anatomical outflow obstructions, indwelling catheters, instrumentation, neurogenic bladder, or a combination of these [165]. There are rare reports of bladder rupture during pregnancy associated with underlying diseases such as necrotizing cystitis [166], during (prolonged) vaginal labor or a trial of labor following CS.

Vaginal Delivery and Puerperium

Intraperitoneal urinary bladder rupture following vaginal delivery is usually seen in association with uterine rupture, while isolated intraperitoneal bladder rupture following vaginal delivery is less common [167, 168]. Isolated extraperitoneal bladder rupture following vaginal delivery is extremely rare [169, 170]. Intrapartum and postpartum status lead to the poor emptying of the urinary bladder thereby leading to increase the tendency for urinary retention following delivery. Bladder rupture during puerperium can occur either due to its incomplete evacuation from pain or from primary bladder pathology. Thus, adequate post-delivery bladder evacuation is of utmost importance to prevent this complication. Fetal head compresses the distended urinary bladder over pelvic brim and symphysis pubis during forceful uterine contractions which may lead to pressure necrosis of the bladder dome. If the patient is not catheterized, bladder rupture is more likely during labor. Postpartum patients undergoing episiotomy or perineal repair frequently experience voiding difficulties which can lead to urinary retention. Interestingly, as these patients frequently pass a small amount of urine, urinary retention may go unnoticed. The retention may terminate in gross bladder distention and subsequent spontaneous rupture [171].

20.6.2.2 Traumatic Bladder Rupture

Cesarean Section

CS does not eliminate the risk of bladder trauma, as the position of the bladder as an abdominal organ exposes it to risk at the time of surgery. Prior CS is a significant risk factor for bladder injury occurring at the time of a CS, conferring a four to fivefold increased risk over a primary CS [161, 164]. In other words, prior CS accounts for 67–72% of the bladder injuries [161, 164]. In particular, adhesion formation between the bladder and lower uterine segment is likely to be a causative factor, because 34.2% of bladder injuries occurred during the formation of the bladder flap [161, 164]. A large baby (fetal weight > 4000 g) was found to be an independent risk factor for bladder injury [164]. This may cause uterine wound extension with an injury to the bladder. The presence of labor was also found to be an independent risk factor for bladder injury during CS [161, 164]. Moreover, the station of the presenting fetal part greater (deeper) or equal to +1 was an independent risk factor for bladder injury, with an OR of 2.4 [164]. Emergency CS is another significant risk factor for bladder injury, especially in patients with previous CS [161, 172]. A complete list of factors that increase the risk of bladder injury during CS is presented in Table 20.6.

Blunt Abdominal Trauma

The most common causes of blunt abdominal trauma are motor vehicle accidents, falls, and domestic trauma. Urinary bladder ruptures are induced mainly by compression on the inferior abdomen which is extremely rare during pregnancy [174]. This determines a great and sudden pressure on the abdominal wall which spreads to the bladder, projects itself on the posterior wall of the pelvis and due to its resistance, and comes back toward the bladder (anterior), giving it a counterblow. To this mechanism, a

Table 20.6 Conditions prone to bladder injury during Cesarean section

Prolonged labor with distended bladder
Obstructed labor
Post-Cesarean pregnancy
Postmyomectomy pregnancy
Postlaparotomy pregnancy
Altered anatomy or fibrosis
Direct extension of disease
History of uterine perforation, septic abortion
Presenting fetal part deeper than or equal to +1
Fetal weight > 4000 g
Well effacement and dilatation of cervix
Preterm Cesarean section where lower segment is not well formed
Cesarean hysterectomy
Ruptured uterus may also be combined with bladder injuries
Placenta percreta may penetrate the bladder

Reproduced with permission from [173]

series of favorable conditions which may contribute to the extent of the lesions can be variable. The amount of urine present inside the bladder at the moment of injury plays an important part. If the bladder is empty, it can be torn only through direct impact of the trauma agent on its walls because of its deep location in the pelvis and its protection by pelvic bones. Full bladder comes out of that protection and becomes an intraperitoneal organ. Bladder wall grows thinner in proportion to the quantity of urine and the flexibility of its muscular fibers decreases. Anatomical areas with least resistance are the superior and posterior walls (dome of the bladder). Vesical pathologies which determine a decline in wall strength (inflammatory, tumor, scarring processes) favor surprisingly serious lesions following minor traumas. Neurological lesions of vesical wall lower its ability of distention and also muscle tone and consequently allow an accumulation of a great amount of urine. It is the case of neurogenic bladder patients. In pregnancy, the raised estrogens cause marked hyperemia, vasodilatation, and increased tortuosity of the blood vessels of the genitourinary system. Moreover, the gravid uterus, as it grows, mechanically lifts the bladder into the abdomen and more anteriorly thus making it more susceptible to injury, either spontaneous or inflicted.

20.6.3 Clinical Presentation

The diagnosis of the uroperitoneum is a difficult one, and there are cases when many experienced surgeons cannot tell for certain if they are facing an uroperitoneum. Pulse rate is commonly over 100 bpm; blood pressure is commonly below 110/70 mmHg [170, 175]. Difficulties in passing urine in postpartum period do occur, but the history of oliguria or anuria with abdominal pain should raise a suspicion of bladder injury. Abdominal pain is located in the lower abdomen (initially), and low back pain can be present. Abdominal examination reveals distended abdomen with dullness on percussion. Signs of peritoneal irritation or peritonitis could be absent initially but are found during first 1–4 days after bladder injury [176]. Low abdominal pain can temporary improved with the placement of a Foley catheter and can worsen over subsequent days, especially when the Foley catheter is removed [177]. Blood on the external meatus or gross hematuria is common with bladder rupture or larger perforation. Even though no history of trauma may be apparent, bladder trauma should be suspected in cases of unexplained hematuria during pregnancy. Unfortunately, the nulliparous women may confuse hematuria with lochia. Fever is not present initially [175]. Per vaginal examination reveals healthy episiotomy wound (if made), lochia rubra, and closed internal cervical ostium [170, 175].

Presentation of an unrecognized bladder injury during CS can lead to vesicovaginal fistula and vesical calculi, meaning without urinary incontinence secondary to a vesicouterine fistula [178, 179]. These patients can present with gross hematuria even several years after CS [180]. In cases of the nonoperative cause, such as inflammatory bowel diseases, the patient can present as recurrent UTI during pregnancy, such as hemorrhagic cystitis despite antibiotic prophylaxis [181].

Bladder injury can be recognized during CS with findings that suggest bladder perforation: the extravasation of urine, a visible laceration, the appearance of a Foley catheter, a sudden increase in bleeding from the wound, and the presence of bloody urine in the urinary bag. Intraoperative intravesical instillation of methylene blue or indigo carmine through the Foley catheter reveals the perforation and its location.

20.6.4 Differential Diagnosis

Due to commonly nonspecific symptomatology, the diagnosis has rarely been suspected initially [182]. Acute renal failure is a most challenging clinical problem when it occurs in pregnancy. As in all patients who develop acute renal failure, prerenal and obstructive causes must be excluded. A particularly important cause of prerenal azotemia in pregnancy is uterine hemorrhage, especially if it is unsuspected as in placental abruption. Infectious causes of acute renal failure in the pregnant woman include acute pyelonephritis and septic abortion. The clinical presentation of both these conditions should be apparent, and appropriate diagnosis and treatment can then be promptly instituted. Renal cortical necrosis is another cause of renal failure that occurs more frequently in pregnancy, and it must be differentiated from the many causes of acute tubular necrosis that may be associated with pregnancy. Postpartum renal failure in previously healthy subjects is associated most often with preeclampsia and/or hypertension, HELLP syndrome, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura [183]. Renal hypoperfusion due to a renal vascular occlusion should be excluded by Doppler ultrasound. The normal platelet count and hemoglobin levels exclude a pregnancy-associated microangiopathy, such as hemolytic uremic syndrome.

Another most common working diagnosis in patients with acute postpartum pain is spontaneous uterine rupture (see Chap. 16) [170] because induced vaginal delivery increases the rate of intraperitoneal bladder rupture commonly associated with uterine rupture [167, 168]. The list of differential diagnoses is summarized in Table 20.7.

Table 20.7 Differential diagnosis of spontaneous bladder rupture

Acute renal failure
Spontaneous uterine rupture
Urinary tract infection
Placental abruption
Acute pancreatitis
Postpartum hemorrhage
Small bowel injury
Large bowel injury

20.6.5 Diagnosis

20.6.5.1 Laboratory Findings

Profound disturbances in serum electrolytes and acid-base status (elevated serum urea, creatinine, and potassium, decreased serum sodium and CO_2 content, and development of metabolic acidosis) are consistent findings among patients with intraperitoneal bladder rupture. When urine enters the peritoneal cavity, reverse autodialysis occurs. Urea and creatinine diffuse down their concentration gradients into the blood. The rapid early rise in creatinine suggests peritoneal urinary resorption (pseudo-renal failure) rather than true acute renal failure. The serum urea and creatinine are elevated in 45% of patients who present within 24 h of bladder rupture and in nearly 100% of the patients who present 24 h after bladder rupture, with higher urea levels due to greater peritoneal absorption [184].

> The hyponatremia associated with elevated serum creatinine levels otherwise consistent with dehydration and renal failure should suggest the diagnosis of urinary peritonitis [166].

Biochemical analysis of ascitic fluid confirms urine by testing ascitic fluid creatinine which is similar to urine creatinine [175].

> Features common to intraperitoneal bladder rupture are (1) urinary ascites, (2) paralytic ileus, (3) acute renal failure secondary to systemic reabsorption of urea and creatinine, (4) hyperkalemia due to acute renal failure, and (5) metabolic acidosis [171].

20.6.5.2 Imaging Modalities

Ultrasound and saline sonocystography are not very sensitive in the diagnosis of bladder rupture. Ultrasound is helpful if the patient had a previous ultrasound with normal findings, and in the case of intraperitoneal rupture, free fluid in the abdomen should raise a suspicion. If bladder rupture is suggested by clinical findings or by radiologic findings (e.g., pelvic ring disruption, obliteration of pelvic fat planes), then a retrograde cystogram with a maximally distended bladder and a post-evacuation film, as a minimum, should be obtained. Through Foley catheter, at least 250–300 ml of contrast material into the urinary bladder is instilled (as much as the alert patient will tolerate). Though retrograde cystography is considered the investigation of choice for establishing the type of bladder rupture in stable nonpregnant cases, contrast studies are avoided during pregnancy for fear of fetal risk.

In general population, CT cystography has the same sensitivity of approximately 90% as plain X-ray cystography, although it is recommended to rule out other visceral injuries [185]. CT cystography can be done in the patient even with impaired renal functions. It is done by retrograde administration of about 300–350 ml diluted (10%) contrast with saline into the urinary bladder through urethral catheter followed by CT scanning of the lower abdomen and pelvis. It detects the site of rupture and even small rent due to bladder distention. However delayed contrast CT scan in excretory phase will not show extraluminal contrast extravasation through the small bladder rent which is usually sealed by a blood clot or omentum [171, 186]. Furthermore, if oral contrast should be given for bowel opacification, it may obscure and confuse the findings when a subsequent plain-film cystogram is needed. The one exception is the potentially unstable patient, where the contrast should be diluted to 5% and instilled into the bladder before any CT cuts are obtained. Air can be used as a substitute bladder contrast agent.

20.6.5.3 Cystoscopy

In pregnancy, to eliminate the radiation to the fetus, if isolated urinary bladder injury is anticipated, cystoscopy can define the location and size of urinary bladder injury instead of retrograde cystography. Cystoscopy is indicated if gross hematuria is experienced after induction of labor [167]. If the enterovesical fistula is suspected, cystoscopy can reveal the presence and location of the vesical fistulous opening [181]. Enterovesical fistula can be confirmed by charcoaluria following oral charcoal administration [181]. Even amniotic sac protrusion can be seen through the vesicouterine fistula.

20.6.6 Treatment

20.6.6.1 Spontaneous Bladder Rupture

Extraperitoneal Bladder Rupture

Extraperitoneal ruptures can mostly be managed conservatively with catheter drainage of the bladder.

Intraperitoneal Bladder Rupture

Intraperitoneal ruptures of the urinary bladder require urgent surgical repair. At emergency laparotomy, the rupture site is identified, sometimes immediately, sometimes with methylene blue over Foley catheter. The laceration is closed in two layers with absorbable sutures, and a retropubic drain and Foley catheter placed. Early management reduces infectious complications with no adverse outcomes [171].

Combined Bladder and Uterine Rupture

After a Pfannenstiel incision, further procedure depends whether the fetus has been delivered. If the fetus is still in the pelvis, it should be delivered first. It can be outside of the uterus, or only part of the fetus can lie outside the uterus. Even the fetus can go first through the rent of the uterus and then through the rent in the urinary bladder. In this situation, the bladder is opened completely, and the fetus delivered from inside the bladder (Fig. 20.17a). In such situations, the posterior wall of the bladder and the anterior wall of the uterus had ruptured (Fig. 20.17b). Both ureteral orifices should be catheterized with a 5Fr feeding tube to confirm clean urine coming out bilaterally. Afterward, the laceration of the posterior bladder wall is closed in two layers with absorbable

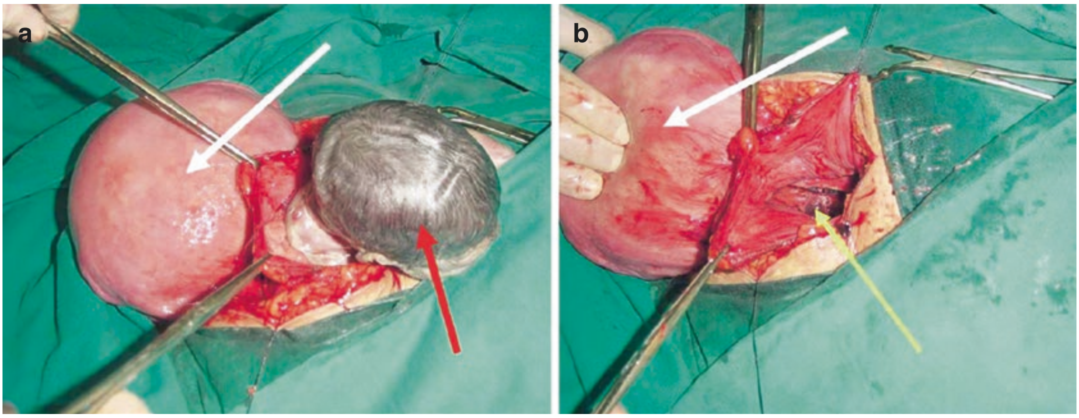

Fig. 20.17 (**a**) Dead fetus in the bladder. Uterus (*white arrow*) and head of the fetus (*red arrow*). (**b**) Rupture of posterior bladder wall and uterus. Uterus (*white arrow*); Rupture site (*yellow arrow*). Reproduced with permission from [167]

sutures, and a retropubic drain and Foley catheter placed. The uterus is then reapproximated using a two-layer closure technique [167].

20.6.6.2 Traumatic Bladder Rupture

Cesarean Section

An isolated small tear at the bladder dome can be sutured primarily, and no additional evaluation is required. A larger tear may be associated with a concomitant injury to the ureter, particularly if damage involves the posterior bladder wall, approximates the ureteral orifice, or is associated with the lateral extension of the uterine incision. In these cases, ureteral catheterization is advisable, even at the cost of expanding the primary bladder tear toward the trigone to identify the orifices clearly.

Most bladder tears detected intraoperatively are repaired with a two-layer running absorbable sutures. The size of the suture should be 2–0 and 3–0. The first bite can incorporate all layers including bladder mucosa, although many omit the bladder mucosa and include only the submucosa and muscular layers. The second imbricating layer may be either a parallel Lembert or a perpendicular Connell stitch. Injuries involving ureteric orifices and the trigonal area may require ureteric stenting, ureteroneocystostomy, etc. For large ruptures, after repair, a suprapubic tube is recommended, but a large urethral catheter would be sufficient for smaller injuries. Safe practice is to keep an indwelling urethral catheter for 10–14 days to keep the bladder compressed. If the suprapubic catheter is also inserted, then one safe guideline could be to start clamping of the suprapubic catheter on the 10th day and remove it on the 12th day. Urethral Foley's catheter is to be removed on the 14th day. Antibiotics should be based on the efficacy against *E. coli* which is the most common pathogen in the female population. Until the patient is febrile and cannot tolerate peroral feeding, i.v. antibiotics are used, and then peroral antibiotics continued. There are no recommendations and guidelines for specific antibiotic therapy and duration of antibiotic therapy in the pregnant population with urinary bladder rupture.

Blunt Abdominal Trauma

Bladder contusions and most extraperitoneal ruptures can usually be managed conservatively with continuous bladder drainage for 7–10 days [187]. Most intraperitoneal and extensive extraperitoneal ruptures need surgical repair [187] with the same surgical principles previously described, no matter the cause. Antibiotics should be commenced immediately when urinary peritonitis with the continuation of pregnancy is suspected or proven. Suppression of the inflammation lowers the production of prostaglandins which in turns lowers the possibility of spontaneous abortion or preterm labor (see Chap. 23).

20.6.7 Prognosis

It is important that the diagnosis is made perioperatively to avoid re-intervention and readmission, which increase the cost and morbidity. Neither severe postoperative complications nor sequelae were noticed after managing the bladder injuries.

20.7 Renal Artery Aneurysm Rupture

20.7.1 Incidence

Spontaneous intra-abdominal and retroperitoneal bleeding during pregnancy is a relatively uncommon event. The most frequent cause of bleeding in this setting is rupture of a splenic artery aneurysm (see Chap. 9). The first published report of ruptured renal artery aneurysm (RAA) was in 1770 by Ludovici Rouppe, who described the case of a sailor who fell onto his right flank and after 9 days felt significant pain and died due to (pseudo)aneurysm rupture [188]. The first clinical case in pregnancy in 1926 was by Chisholm [189]. At the time when most of the information on this disease came from autopsy cases rather than angiography, it was considered to be extremely rare in general population with the incidence of 0.01–0.09% [190]. With the introduction of visceral angiography, the diagnosis of RAA became more frequent (0.09–2.5%). However, these figures do not reflect the true incidence of RAA in the general population because the symptoms that brought these patients to renal angiography may have been caused by the presence of an RAA. Cohen and Shamash summarized the cases in pregnancy during the period 1926–1987 [191], and Lacroix added patients up to 2001 with a final number of 26 patients [192]. Until 2016, 32 cases during pregnancy have been reported in English literature [193]. Prior to 1970, reported rupture of RAA occurred most often on the left side and during the third trimester, while during the period 1970–1996, reports have not shown a left-sided predominance [194]. It is possible that the higher incidence credited to pregnant patients may be due to the fact that a case occurring during pregnancy is of unusual interest and is perhaps more likely to be recorded than one in a nonpregnant woman. Review from 2016 shows RAA in the third trimester in 68.7%, only several cases in the postpartum period, and never during labor [193].

20.7.2 Etiopathogenesis

Over 50% of ruptured arterial aneurysms in women under the age of 40 are pregnancy related [195]. The origin of RAA during pregnancy is multifactorial and not fully understood because the data are sparse. Although pregnancy is probably not associated with an increased incidence of RAAs, it is associated with a higher rate of rupture.

Risk Factors for RAA Rupture:

- Incomplete calcification
- Size >2 cm (no firm proofs [190])
- Progressive enlargement
- Renal embolization
- Severe hypertension
- Pregnancy especially in the third trimester [196]
- Patients wishing to become pregnant

Up to 1997, the proportion of patients during pregnancy and puerperium in all surgically treated ruptured RAA was 59% [190]. Some of these lesions may result from congenital defects in the elastic tissue of the media, from arteriosclerosis especially in older patients, from postinfectious or post-traumatic lesions, or from fibromuscular dysplasia [197]. Fibromuscular dysplasia can cause both stenosis and aneurysmal dilatation of the renal artery and occurs most frequently in young women. Patterson reported the presence of "muscular intimal thickening" just proximal to the aneurysmal region in a renal artery that ruptured during pregnancy [198]. When associated with fibromuscular dysplasia, RAA can be found bilaterally in 7–30% and multiplies unilaterally in 7–13% and extrarenally in 2.5–10% [199]. Positive family history is also a risk factor [200]. Hemodynamic changes such as increased intravascular volume, increased cardiac output, and increased intra-abdominal pressure in pregnancy, as well as hormonal changes, predispose to

rupture [191] as in splenic artery aneurysms (see Chap. 9). The increased risk in the third trimester of pregnancy is due to [201] (1) expanded intravascular volume and increased blood pressure, (2) increased intra-abdominal pressure, (3) weakened structure of the major arteries following increased steroid production, and (4) physiological clockwise rotation of the enlarged gravid uterus which may compress the aorta and the right renal artery, thus increasing pressure on the left renal artery.

The mechanism of RAA rupture in the first trimester of pregnancy remains unclear. The renal plasma flow and glomerular filtration rate in pregnant women in the first trimester rapidly increase to about 30–50% above the nonpregnant level; thus, increased blood flow to the kidneys may increase the pressure in the arteries, resulting in RAA expansion and rupture [202]. Multiple pregnancies might cause irreversible vessel wall damage, which promotes a rapid increase in aneurysm size, subsequently causing rupture [203]. Moreover, RAAs can thrombose or release emboli which subsequently obstruct smaller renal arteries causing multiple renal infarctions.

20.7.3 Clinical Presentation

Diagnosis of rupture RAA during pregnancy is difficult as there is no pathognomonic sign or presentation. Clinical presentation differs between ruptured and unruptured RAA. Typically the patient with an RAA is asymptomatic. If symptomatic, the patient complains of vague flank or upper abdominal pain that can progress to more severe pain due to enlargement of the RAA. When RAA rupture occurs during pregnancy, the clinical presentation is easily confused with those more common conditions like placental abruption or uterine rupture. Most patients complain of acute, severe flank pain, some complain of solely abdominal pain, while some have both flank and abdominal pain commonly fainting attacks [204]. It is called *Wunderlich syndrome*, in which spontaneous nontraumatic renal hemorrhage occurs into the subcapsular and perirenal spaces. Collapse is present with large retroperitoneal hematomas. Sometimes there is a tamponade effect of the retroperitoneum. There is no associated history of trauma or fever [205], but hematuria can be present. Gross hematuria and clot retention have been reported as a sign of intraparenchymal RAA rupture into the collecting system, renal embolization, or infarction [206]. Therefore, Wunderlich syndrome is clinically characterized by the *Lenk's triad*:

- Acute flank pain
- Flank mass
- Hypovolemic shock

Physical findings in the absence of rupture may merely reveal hypertension, present in 15–75% of patients [207, 208], or, in some cases, abnormal pulsations or bruits. There are no symptoms and signs of labor or vaginal bleeding, and cervix is closed and uneffaced [205]. If the bleeding is severe, the patient is pale and hypotensive with tachycardia [205]. On abdominal examination generalized [205] or localized tenderness is found. Tender mass can be found on affected side [198], and if the retroperitoneal mass/hematoma is large, it may displace the gravid uterus to the opposite side [209]. Uterus corresponds to the duration of pregnancy. Depending on the duration and severity of bleeding/retroperitoneal hematoma, fetal cardiac activity can be absent [205] or present.

20.7.4 Differential Diagnosis

Unfortunately, many cases initially present without abdominal tenderness or guarding and normal vital signs, so that renal colic may be suspected. Differential diagnosis depends whether the symptoms and signs of blood loss are present (Table 20.5). With the increasing fetal distress or signs of hemodynamic instability, a differential diagnosis of placental abruption or uterine rupture is commonly considered.

20.7.5 Diagnosis

Most of the cases are discovered incidentally. During the first half of the twentieth century, the significant number was diagnosed at autopsy.

20.7.5.1 Laboratory Findings

Laboratory findings in the unruptured RAA reveal microscopic hematuria in 33–45% of cases [208, 210, 211], whereas in ruptured RAA, anemia is frequently encountered and microscopic hematuria is present in most cases [204].

20.7.5.2 Transabdominal Ultrasound

Transabdominal ultrasound is the first imaging method of choice in both stable and unstable patients. Without the Doppler mode, intrarenal uncalcified RAA can be mistaken for hydronephrosis (Fig. 20.18). A Doppler ultrasound examination can define location and dimension of the RAA (Fig. 20.18) and also confirms arterial patency and active bleeding if present [200, 212].

20.7.5.3 CT Angiography

Abdominal CT with or without contrast is rarely performed for the patients with lumbar pain because abdominal sonography is adequate for the diagnosis. Abdominal CT with i.v. contrast is commonly performed after preterm delivery or CS when a definitive diagnosis is still unknown. CT angiography defines the location of the bleeding, characteristics of RAA, and the extension of the hematoma (Fig. 20.19). The downside of this imaging method is that it cannot be used for selective embolization or stenting of the ruptured RAA.

20.7.5.4 Angiography

Digital subtraction angiography precisely defines the location of an aneurysm and the location of rupture with leakage (Fig. 20.20). In the same act the stent graft can be placed over an aneurysm covering the rupture site if indicated (see Sect. 20.7.6.2).

20.7.5.5 Abdominal MR

Abdominal MR is rarely performed because it is unavailable in many institutions in emergency settings [213] and it is not suitable for hemodynamically unstable patients. Abdominal MR (Fig. 20.21), without contrast, is used when symptomatic, unruptured RAA is present [200].

20.7.6 Treatment

20.7.6.1 Conservative Treatment

When asymptomatic RAA is diagnosed during pregnancy conservative treatment could be indicated if [204]:

- Non-calcified
- <2 cm in diameter
- Not increasing in size
  The presence of contralateral kidney

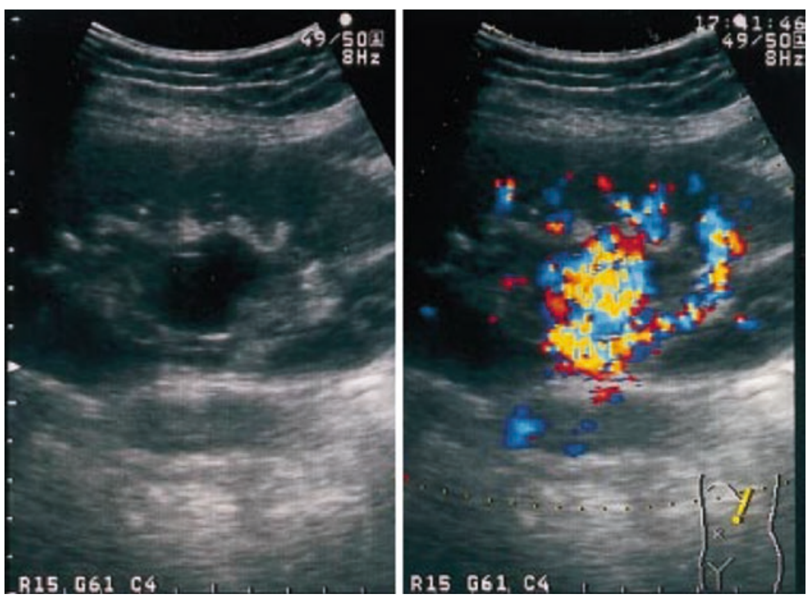

Fig. 20.18 Ultrasonogram of the left kidney showing "hydronephrosis" (*left*). A color Doppler scan in the same plane showing an intrarenal aneurysm (*right*). Reproduced with permission from [212]

Fig. 20.19 Abdominal CT with i.v. contrast showing a left renal artery aneurysm (*white arrow*) and a large retroperitoneal hematoma (*white star*). Reproduced with permission from [193]

Fig. 20.20 Left renal artery angiogram revealing an aneurysm, 2 × 3 cm, with leakage. Reproduced with permission from [193]

Raised blood pressure should be lowered to lessen the possibility of RAA rupture.

20.7.6.2 Endovascular Treatment

There are two endovascular procedures used: embolization and placement of the stent graft. The location of an aneurysm is important because embolization of an aneurysm of the main renal artery or at the bifurcation carries a high risk of complete occlusion of the renal artery and atrophy of the kidney [216] with the loss of the kidney. The elective endovascular management does not reduce

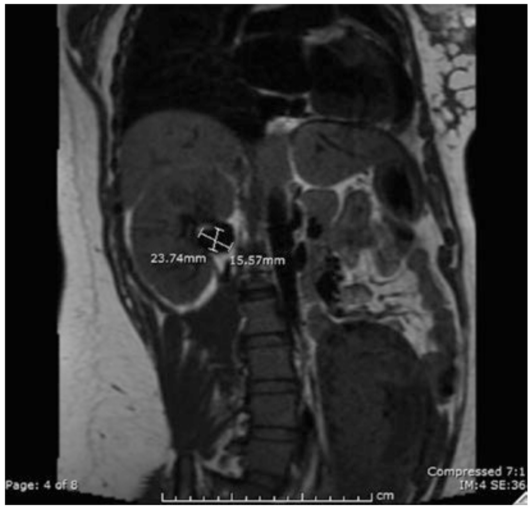

Fig. 20.21 MRI angiogram at 26 weeks of pregnancy showing a right RAA (2.4 cm × 1.6 cm). Reproduced with permission from [200]

in-hospital mortality when rupture of the RAA is diagnosed in general population, although it allows a lower rate of complications and shorter length of stay [214]. Endovascular embolization has been successfully performed for ruptured RAA in pregnancy [201, 213, 215]. Ideally, stent and coils covering the RAA should be used. If this is technically not possible, embolization of the main renal artery in hemodynamic instability could stabilize the patient with subsequent nephrectomy [197].

The lower success rate, stent migration, or leakage is present in the pregnant population [193] as in general population. Unsuccessful stent placement could lead to nephrectomy as the only option in complicated settings [193]. The open repair (see Sect. 20.7.6.3) should be considered as the method of choice, considering the young age of women to avoid nephrectomy, or eventually endovascular techniques could be used as the bridge therapy until delivery.

20.7.6.3 Obstetric Management

Cesarean Section

Indications for emergent CS are for obstetric indications. In many cases due to rapidly increasing severe maternal pain and sudden fetal distress, uterine rupture or placental abruption is suspected [193].

Prevention and Treatment of Preterm Labor

See Chap. 23.

20.7.6.4 Surgical Treatment

Anesthetic and Perioperative Management

Most patients have raised blood pressure before RAA rupture. During the episode of rupture, the blood pressure drops. It is important that postoperative (postinterventional) blood pressure is maintained in the normal range to minimize postoperative complications. If significant blood loss is present, it should be restituted with packed blood cells to minimize ischemic consequences of the fetus (and the mother). For other anesthetic and perioperative principles, see Chap. 21.

Operative Principles

On laparotomy a large retroperitoneal hematoma is found on affected side; extension depends on the duration and the severity of bleeding. It can expand from below the diaphragm to the pelvis and can even cross the midline [205]. The hematoma is non-expanding and non-pulsatile [205]. It is justified to save an organ without increasing the surgical risk for the patient. In the setting of ruptured RAA, information on preoperative renal function is usually incomplete.

There are several reconstructive options: (1) aneurysmal resection and a direct end-to-end anastomosis (Fig. 20.22) and (2) extracorporeal vascular reconstruction with autotransplantation. The salvage of the kidney in the emergency situation bears no additional surgical risk and can be performed without extending the duration of surgery significantly. If the RAA is large and the kidney completely damaged, the (partial) nephrectomy is the only option.

In 1960, the mortality for nephrectomy in all groups of patients with RAA was 5.3–6%, whereas organ-preserving methods had a mortality of 53–60% [217]. It was not until 1981 that Love et al. reported the first case of organ-preserving surgery in a pregnant patient with RAA. Up to 2001 salvage of the kidney had been reported in 26% of cases, either by in situ repair of the renal artery or by ex situ repair and autotransplantation of the kidney [192]. Since then endovascular treatment has been successfully performed [201, 213, 215].

20.7.7 Prognosis

20.7.7.1 Maternal Outcome

Before 1956 maternal mortality of ruptured RAA was 100% [190]; up to 1987 in the English language literature, maternal mortality of ruptured RAA in pregnancy was reduced to 56% [204]. Until 1997 maternal mortality was further reduced to 8% [190]. It is important to note that in the period 1926–1997 the survival rate of surgically treated ruptured RAA in general population was 74.4% (29/39) [190], and all deaths were during pregnancy. Analysis of complete period 1926–2016 claims maternal mortality of 34.4% [193].

20.7.7.2 Fetal Outcome

Fetal mortality is higher than maternal mortality. Before 1956 fetal mortality was 100%, during the period 1927–1987, it was lowered to 82% [191], and in the period 1956–1997 it was further reduced to 62% [190]. Analysis of cases up to 2016 shows further decline in fetal mortality. Analysis of complete period 1926–2016 claims fetal mortality of 59.4% [193].

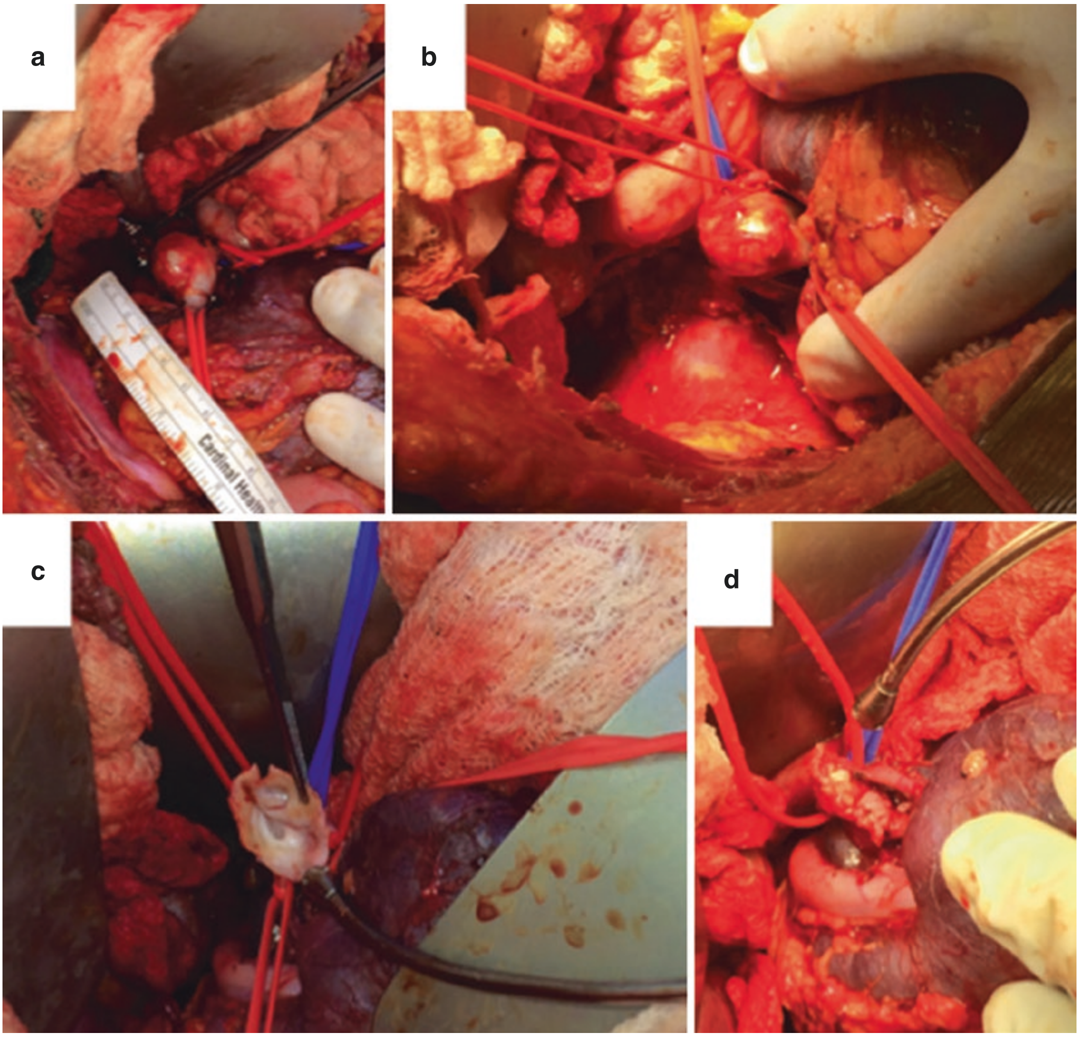

Fig. 20.22 Intraoperative pictures of RAA before and after the primary repair. (**a**, **b**) The RAA in the right renal hilum. Red vessel loops were placed proximally and distally to the RAA around the right renal artery. (**c**) After careful dissection of the RAA, it was noted to be saccular in nature. (**d**) Right renal artery after the primary repair of the RAA. *RAA*, renal artery aneurysm. Reproduced with permission from [200]

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21 Anesthetic and Perioperative Management

Abstract

In order to provide safe anesthesia for the mother and fetus, the following goals should be reached: (1) optimization and maintenance of normal maternal physiological function, (2) optimization and maintenance of uteroplacental blood flow and oxygen delivery, (3) avoidance of unwanted drug effects on the fetus, (4) avoidance of stimulating the myometrium (oxytocic effects), (5) avoidance of maternal awareness during general anesthesia, and (6) use of regional anesthesia, if possible. Antibiotics and thromboprophylaxis are the most common medications administered for acute abdomen during pregnancy. Antibiotics should be administered according to the FDA drug classes. Anesthetic management is especially difficult in patients with abdominal trauma or polytrauma when in addition to hemorrhagic shock there are problems with patient's airway management. Preoperative and postoperative fetal monitoring is important for early recognition of fetal distress which influences the timing and type of combined obstetric and surgical intervention.

21.1 Anesthetic Management

In order to provide safe anesthesia for the mother and fetus, the following goals should be reached:

- Optimization and maintenance of normal maternal physiological function
- Optimization and maintenance of uteroplacental blood flow and oxygen delivery
- Avoidance of unwanted drug effects on the fetus
- Avoidance of stimulating the myometrium (oxytocic effects)
- Avoidance of maternal awareness during general anesthesia
- Use of regional anesthesia, if possible

21.1.1 Anesthetic Medications

Anesthetic concerns in the pregnant patient can be broken down into two major categories: teratogenicity of the anesthetic agents and maternal physiological changes as a result of anesthetic agents.

The teratogenicity of anesthetic agents, defined as the potential effect in chromosomal damage or in carcinogenesis in the fetus, is minimal and any morbidity to the fetus is considered to be primarily from the underlying disease, not the anesthetic agent [1, 2]. Large studies found no increase in congenital anomalies with different types of anesthesia used in surgery during pregnancy [3, 4]. In a consensus statement published in the *New England Journal of Medicine* in 2000, no anesthetic agents were listed as definitively causative of fetal malformations [5]. While

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_21

Table. 21.1 List of common anesthetic drugs and their classification as per FDA category

Drug	FDA category
Bupivacaine	C
Lignocaine	B
Butorphanol/nalbuphine	C (in small doses)/D (in high doses)
Succinylcholine	C
Rocuronium	C
Thiopentone sodium	C
Propofol	B
Morphine/meperidine/fentanyl	B (in small doses)/D (in high doses)
Sufentanil/remifentanil	C

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no clinical data currently link cellular actions with teratogenic outcomes, their theoretical risk should not be completely disregarded. Many agree that surgery during the first trimester, the period of organogenesis, should be avoided if not emergent [2, 6, 7]. Table 21.1 shows the list of common anesthetic drugs and their classification as per FDA category.

When considering the possible teratogenicity of various anesthetic agents, several important points must be kept in mind. First, the background incidence of congenital anomalies in humans is approximately 3%. Second, physiologic derangements such as hypoxemia, hypercarbia, stress, and hypotension may be teratogenic themselves. These problems can occur during anesthesia and surgery and sometimes exist preoperatively [9].

The drugs crossing placenta may be categorized into three types. In type 1 (e.g., thiopental), the complete transfer occurs with equilibrating concentrations in maternal and fetal blood. In type 2 (e.g., ketamine), the drug reaches a higher concentration in fetal blood compared to maternal blood. In type 3 (e.g., succinylcholine), only minimal amount reaches the fetal blood (Table 21.2).

21.1.1.1 Sedation

Sedation in pregnancy has always been a challenge to anesthetists. Sedation during ERCP in pregnant patients has important aspects of fetal and maternal monitoring and side effects of the prone position [10, 11]. Following electrocardiography, noninvasive blood pressure measurement, pulse oximetry, and fetal heart rate monitoring devices are applied. Insufflation of oxygen at a flow rate of 6 L/min is maintained throughout the procedure. The patients are placed in a left lateral to prone position. Fetal shielding is accomplished with a lead apron placed between the radiation source and the patient. Although there are no proofs of teratogenicity in humans for anesthetic drugs, inhaled or local, all agents that are administered during pregnancy must be used with caution and vigilance. Currently, the best options are propofol, midazolam, and fentanyl. Propofol as a short-acting agent is preferred because it can be titrated easily and has a good recovery, with a low incidence of nausea and vomiting. Alternatively, midazolam can be used because of its specific amnesic and anxiolytic properties. The analgesic component of this sedation regimen is the opioid. All drugs are given in incremental doses to prevent hemodynamic and respiratory changes in the mother and fetus during the procedure. The most commonly conscious sedation is achieved and maintained with intravenous midazolam 3–5 mg and duodenal hypomotility induced by hyoscine-*N*-butylbromide 20 mg [12].

21.1.2 Airway Management

Airway management becomes particularly problematic in the parturient due to the normal physiologic changes that take place during pregnancy. Increased oxygen consumption and mechanical displacement of the abdominal organs cause the pregnant patient to increase minute ventilation, primarily through a 30–40% increase in tidal volume [13]. A compensatory respiratory alkalosis with a $PaCO_2$ from 30 to 35 mmHg develops. End-tidal CO_2 monitoring should be used intraoperatively.

The success of regional anesthesia in this population owes its popularity mainly to the airway complications that general anesthesia entail. Airway complications are more prevalent in a

Table. 21.2 The placental transfer characteristics of commonly used anesthetic drugs

Drug	Properties	Placental transfer	Remarks
Induction agents			
Thiopental	Highly lipid soluble, weak acid	+++	Quickly cleared by neonate after delivery
Propofol	Lipid soluble	+++	Transient depression of Apgar score and neurobehavioral effects in neonate
Ketamine	Weak base	++++	F/M ratio 1.26 occurs within 2 min of intravenous bolus
Inhalation agents			
Volatile anesthetics	Highly lipid soluble; low molecular weight	+++	Greater sedative effect on neonate if dose-delivery interval is prolonged
Nitrous oxide		++	Possible diffusion hypoxia in neonate
Opioids			
Morphine	Less lipid soluble; but low protein binding	++	
Fentanyl	Lipid soluble	+++	
Pethidine	Only 50% plasma protein bound	++	Prolonged neonatal depression due to increased half-life of meperidine and its metabolite—Normeperidine
Remifentanil		+	No adverse fetal effects as rapidly metabolized by fetus
Naloxone		+++	Though short-term safety of naloxone is well documented, it should be used only in cases of absolute or relative maternal opioid overdose
Benzodiazepine	Highly lipid soluble	++	More neonatal depression; midazolam—less placental transfer than diazepam
NM blockers	Large molecules; poorly lipid soluble; highly ionized	–	No significant clinical effects on fetus
Anticholinergics			
Atropine	Lipid soluble; tertiary amine	++	
Glycopyrrolate	Fully ionized; quaternary ammonium compound	–	
Neostigmine	Quaternary ammonium compound; but a small molecule	+++	May cause fetal bradycardia: Hence it is better to add atropine to neostigmine in incidental surgery during pregnancy
Local anesthetics			
Lignocaine	Less lipid soluble; low protein binding	++	Can accumulate in the fetus due to "ion trapping" if the fetus becomes acidotic
Bupivacaine; ropivacaine	Highly lipid soluble; but high protein binding	++	

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parturient receiving general anesthesia than those having regional techniques [14]. Unique issues to the gravid patient in airway management are:

- Increased risk of aspiration due to delayed gastric emptying and decreased lower esophageal sphincter tone in combination with increased intra-abdominal pressure.
- Despite safety of rapid-sequence intubation in pregnancy, because of lower serum pseudocholinesterase levels in pregnancy, using a lower dose of succinylcholine during induction is recommended.
- Both depolarizing and nondepolarizing muscle relaxants cross the placenta. Effects of these drugs onto CTG pattern and fetal activity

might lead to a falsely nonreassuring tracing and non-indicated intervention.

> A nasogastric tube should be inserted in a semiconscious or unconscious injured pregnant woman to prevent aspiration of acidic gastric content [15].

Additionally, vascular engorgement of the respiratory tract during pregnancy may lead to tracheal intubation difficulties. Edema in the airways leads to friable tissues and increased potential for bleeding and the necessity of using smaller-sized endotracheal tubes in the parturient [16]. Because decreased lower esophageal sphincter pressure and delayed gastric emptying in pregnancy can cause an increased risk of aspiration, cricoid pressure should be used to prevent aspiration during intubation [17]. Therefore, for the parturient who is facing an emergent abdominal operation with a full stomach, a rapid-sequence intubation is preferred [16]. Also, the underlying cause of acute abdomen, intraoperative strategy, and possible intraoperative complications mandate general anesthesia.

Other compounding airway issues include weight gain, increased breast size, as well as a decreased functional residual capacity, increased oxygen consumption, and the potential for aortal and venocaval compression in the supine position during intubation. All these issues may lead to rapid desaturation, potential lower cardiac output, and placental fetal compromise and asphyxia during delayed attempts at securing the parturient's airway. In addition to these physiologic changes, a disease-induced hypotension in the pregnant patient should be treated initially with aggressive intravenous fluid resuscitation. The patient should be placed in the left lateral decubitus position, if possible, do decompress inferior vena cava to increase venous return (Fig. 21.1).

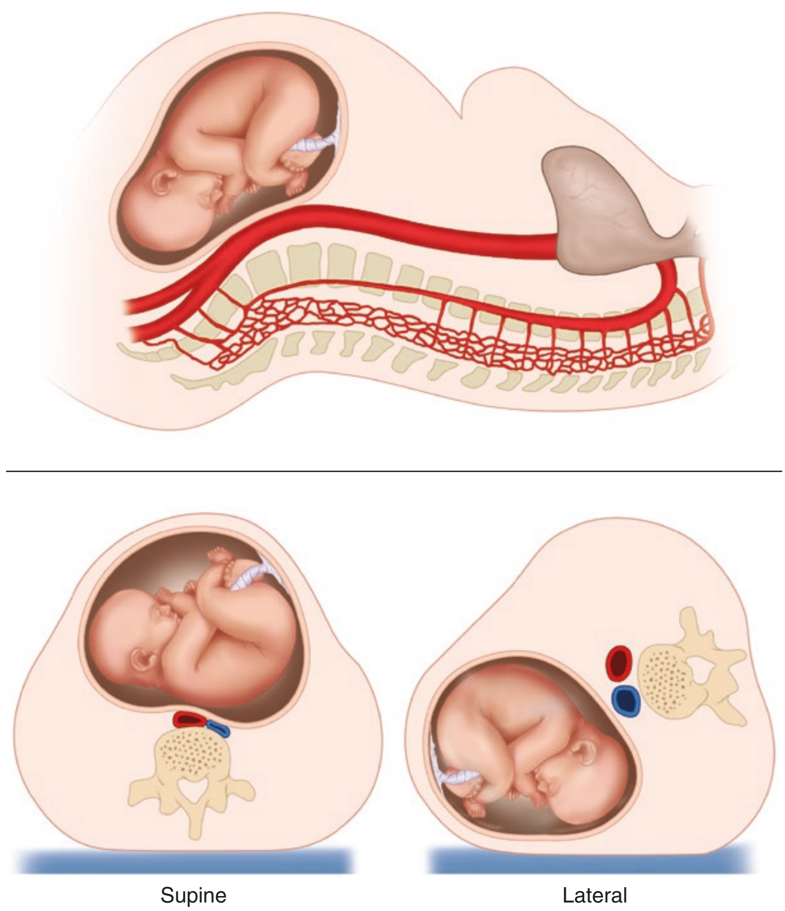

Fig. 21.1 Left lateral tilt in pregnant women during laparoscopic procedures (Reproduced from [18] under the CC BY 3.0)

Trendelenburg positioning can also be used in the hypotensive patient to increase venous return [1].

The preferred type of anesthesia for CS during management of acute abdomen or in the perioperative period is general endotracheal. Hemodynamic stability may be better with general anesthesia and may be of benefit in the presence of sepsis and use of anticoagulants such as heparin. General anesthesia allows greater hemodynamic control and facilitates management of the acid–base status especially in patients receiving epoprostenol for CVVH in acute pancreatitis during pregnancy. Postoperative ventilatory support in ICU permits resolution of the acidosis.

21.1.2.1 Diaphragmatic Hernia

If a hernia is approached through a thoracotomy incision [19], the affected side is placed uppermost. Mediastinal shift, which compromises venous return and collapse of the lower lung, may be worsened by positional compression from the herniated dilated viscera. A rapid-sequence induction is indicated because the patient is at risk of pulmonary aspiration.

Use of general anesthesia and positive-pressure ventilation may be advantageous in patients with a traumatic diaphragmatic hernia to expand the atelectatic lung, increase functional residual capacity, and deliver high concentrations of oxygen. Lung ventilation must be undertaken with low tidal volume or low airway pressure until the abdominal contents have been removed from the chest or until thoracotomy has been performed. The cardiovascular collapse might occur during positive-pressure ventilation. The re-expanded lung previously compressed by herniated viscera may shift mediastinal structures, and venous return may be impeded [20, 21]. Increased pleural pressure from mechanical ventilation is transmitted to the abdomen. It results in increased upward displacement of the viscera toward the diaphragm and may worsen cardiovascular collapse [21]. A surgeon must be ready to operate before ventilation is begun [20].

21.1.2.2 Abdominal Trauma

The literature about obstetric, anesthetic, and surgical management of pregnant trauma victims is limited [22]. The pregnant trauma victim presents a unique spectrum of challenges to the trauma health-care team. The surgical diagnosis may be unknown at the time of incision, as may be the nature and extent of the procedure being undertaken. The fact that pregnancy may not always be known to be present to the health-care team (at the scene of transportation accidents, in the emergency room, or in the operating room) additionally complicates the situation.

> Pregnancy must always be suspected (until proven otherwise) in any female trauma patient of childbearing age [22].

Vasopressors, which are very rarely indicated in trauma patients, should be avoided unless absolutely necessary because of the risk of decreasing uterine blood flow.

> If vasopressors are required, ephedrine should be the first choice as it preserves the uterine blood flow, but there should be no hesitation in using other vasopressors when necessary.

Head and Neck Injury

Women in late pregnancy have difficult airways. Mallampati class 4 airway (with only the hard palate visible and with no view of the soft palate or uvula) increases by 34% between 12 and 38 weeks [23]. The additional fact that these patients have sustained trauma and will likely be in cervical collars simply compounds an already difficult situation [24]. If there is an uncertainty about the integrity of the cervical spine, direct laryngoscopy should be avoided, and fiber-optic (awake fiber-optic) intubation of the trachea, if feasible (time constraints and/or equipment availability), should be considered [25]. If direct laryngoscopy is deemed necessary, an “in-line stabilization” of the head and neck by an assistant to prevent extension and rotation of the cervical spine is indicated. If awake fiber-optic intubation of the trachea is selected, it is essential to titrate analgesic and sedative drugs carefully to maintain continual meaningful verbal communication between the anesthesiologist and the patient.

Respiratory depression and aspiration of stomach contents during the application of a

local anesthetic agent are much less likely to occur if the patient remains awake and alert. In addition, a rational alert mother minimizes the risk of neonatal depression. In patients in anesthesia, once intubation is accomplished, nasogastric decompression should be performed to minimize the ongoing risk of aspiration. Midazolam is the benzodiazepine recommended; however, it is highly unionized and very lipophilic, and its fetal/maternal ratio is 0.76 at 15–20 min after maternal administration. However, unlike other benzodiazepines, the ratio falls rapidly. No adverse fetal effects have been reported [26]. It has been empirically established that trauma victims with a GCS≤8 usually require intubation and mechanical ventilation for both the airway control and control of the intracranial pressure. However, trauma victims with "good" GCS can "talk and deteriorate/die" following traumatic head injury, particularly an injury associated with loss of consciousness, and delayed deterioration has been observed up to 48 h after the initial insult.

The succinylcholine-induced ICP increase has been a concern in the past. Recently, it has been shown that the magnitude and clinical importance of this increase have been grossly exaggerated. It is currently believed that when there is an urgent need to secure an airway in the head-injured pregnant trauma victim, succinylcholine is an appropriate and safe drug, and it should be used. All of the intravenous anesthetic agents (except ketamine) cause some degree of vasoconstriction and therefore decrease cerebral blood flow. All of the inhaled agents have some cerebral vasodilatory effect; however, their administration is usually consistent with acceptable ICP levels [27].

Spinal Cord Injury

The anesthetic management of a spinal cord injury in pregnancy depends upon the site, extent, and duration of the lesion. Complete transection of the cord is usually associated with cardiovascular instability due to either neurogenic shock in the acute phase or subsequent autonomic hyperreflexia. In the latter case, epidural analgesia is often of value by blocking afferent pathways, thereby reducing the stimuli causing paroxysmal sympathetic activity. Parasympathetic pathways are intact and life-threatening bradycardia can occur. Intravascular volume status can be difficult to assess and manage, particularly in acute injury. Intravenous fluid therapy is best guided by the use of central venous pressure monitoring. Careful attention should be paid to the patient's position and the compression of pelvic venous structures by the gravid uterus in order to distinguish between postural hypotension and volume depletion. Maternal hypotension must be avoided both to maintain uterine blood flow and also to avoid secondary ischemic damage in the evolving lesion of the cord. Irrespective of the chosen method of anesthesia, preoperative and postoperative neurological findings should be fully documented.

If radiological evidence suggests that the neurological deficit is caused by edema, the principal anesthetic concern was to avoid secondary (irreversible) cord damage in the mother and enable timely delivery in case of acute fetal compromise. If the patient has a normal airway and other than the cervical collar, there are no reasons for anticipating difficulties with intubation. General anesthesia with in-line stabilization of the neck during intubation is the most appropriate [28].

21.1.2.3 Acute Appendicitis

Pregnant patients with AA, compared to non-pregnant, have similar occurrences of all specific complications except pneumonia, which occurred more frequently in pregnant women (0.7% vs. 0.2%, p=0.004). All cases of postoperative pneumonia were observed in women who underwent general endotracheal anesthesia [29].

21.1.3 Intraoperative CO_2 Monitoring

> Intraoperative CO_2 monitoring by capnography should be used during laparoscopy in the pregnant patient (Level III).

Fetal acidosis with insufflation has not been documented in the human fetus, but concerns over potential detrimental effects of acidosis have led to the recommendation of maternal CO_2 monitoring [30, 31]. Initially, there was a debate over maternal blood gas monitoring of arterial carbon dioxide ($PaCO_2$) versus end-tidal carbon dioxide ($ETCO_2$) monitoring, but the less invasive capnography has been demonstrated to adequately reflect maternal acid–base status in humans [32]. The safety and efficacy of $ETCO_2$ measurements in pregnant women have been confirmed [33–35] making routine blood gas monitoring unnecessary.

21.1.4 Extracorporeal Membranous Oxygenation

Use of extracorporeal membranous oxygenation (ECMO) for the treatment of refractory hypoxemia or cardiac support in trauma has been limited by the difficulties of emergency vascular access, the risk of hemorrhage, and lack of proof regarding benefit. ECMO therapy may be beneficial during pregnancy/in the early postpartum period in H_1N_1-related hypoxemia [36, 37] massive thrombotic/amniotic fluid embolism [38, 39], and peripartum cardiomyopathy [40]. Only one case of successful ECMO therapy for maternal chest trauma has been reported [41]. Therefore this therapeutic option should be considered rescue therapy in the setting of maternal trauma with refractory hypoxemia.

21.2 Medications

Interests of both the mother and the fetus must be considered in therapy during pregnancy. Usually, these interests do not conflict, because what is good for the mother is generally good for the fetus. Sometimes, however, maternal therapy must be modified to substitute alternative but safer therapy because of the concerns about drug teratogenicity (e.g., substituting a histamine2 receptor antagonist for misoprostol, an abortifacient that is contraindicated during pregnancy) [42, 43]. Rarely, the maternal and fetal interests are diametrically opposed, as in the use of chemotherapy for maternal cancer, a therapy that is potentially lifesaving to the mother but life-threatening to the fetus [44]. These conflicts raise significant medical, legal, and ethical issues.

There are many categories of drugs that could have deleterious effects on a fetus, and the detailed elaboration is out of the scope of this book. There are three main categories of medications used in these patients: (1) anesthesiologic medications (see Sect. 21.1.1), (2) prophylactic, and (3) therapeutic. All teratogenic drugs generally determine a specific pattern or single malformation during a sensitive period of gestation with a dose-dependent effect.

21.2.1 Antibiotics

The US Food and Drug Administration has categorized all antibiotics according to the risks associated with their use in pregnancy. Two categories are important:

- Category A: studies in pregnant women do not demonstrate any risks to the mother or fetus.
- Category B: while animal studies show no risk, human studies are inadequate or animal toxicity has been noted, but the studies on humans show no risk.

There are no antibiotics in the category A. FDA category B antibiotics should be administered when the acute abdomen is highly suspected or found (at least 30–60 min prior to skin incision) in all patients (administered to 94% of patients in the literature) [45].

21.2.1.1 Acute Appendicitis

Standard antibiotics in use are second-generation cephalosporins which comprise 60% of all classes of antibiotics used during pregnancy for acute appendicitis (AA) [46]. If a gangrenous or perforated AA is found, cephalosporins and metronidazole are used [47]. Metronidazole use in pregnant patients is still considered controversial with a recommendation against its use during the first trimester of pregnancy. However, there is no increase

in teratogenic risk when used in recommended doses regardless of trimester [48, 49]. The duration of antibiotic therapy should be discontinued as early as possible. If phlegmonous AA is found, single preoperative dose is adequate [50]. In non-pregnant population even operation without antibiotic therapy for phlegmonous AA is adequate. Therefore, a pregnant patient with high suspicion of AA time from admission to the operation should be short as possible, and if during the operation, normal or phlegmonous AA is found, there is no need for antibiotic therapy (except other pathology is found when antibiotic therapy is indicated).

21.2.1.2 Acute Cholecystitis

Penicillins and second-generation cephalosporins (FDA category B) are most commonly used. The first-line treatments are ampicillin and sulbactam or cefoxitin/cefuroxime. There is no consensus on the duration of antibiotic use in pregnancy. Two recommendations from general population can be applied: (1) to use antibiotics until the patient becomes afebrile and does not show evidence of leukocytosis or elevated CRP or (2) single-dose or 24-h therapy in organ-occupying infection is present [50].

21.2.2 Pain Management

Use of NSAIDs during the second and third trimesters is associated with oligohydramnios and anuria and, after 30 weeks of gestation, is associated with an increased risk of premature closure of the fetal ductus arteriosus (Botalli's duct), with subsequent pulmonary hypertension, intracranial hemorrhage, and necrotizing enterocolitis [51–56]. When appendectomy is performed with CS through median laparotomy, then all classes of medications could be used as in nonpregnant patients unless contraindicated for maternal reasons.

NSAIDs were the first-choice treatment for symptomatic relief but with the risk of miscarriage which was the highest with NSAID use around the time of conception and increases with NSAID use for longer than a week [57–59]. Prostaglandins are needed for successful implantation of an embryo into the uterus wall [60] and play an important role in human ovulation and implantation through their own effect and interaction with platelet-activating factors and cytokines, both in the uterus and in the embryo [61, 62]. Suppression of prostaglandin biosynthesis by NSAIDs could, therefore, lead to abnormal implantation with a predisposition for miscarriage [59]. There are also differences of transplacental pharmacokinetic parameters between different NSAIDs. The results suggest that the fetal risk of diclofenac is higher than those of salicylic acid and antipyrine [63]. If indicated, ibuprofen is the preferred agent. Unfortunately, selective NSAIDs (cyclooxygenase 2 inhibitors) are classified as pregnancy category C because of increased peri-implantation and postimplantation losses and reduced fetal survival in rats and rabbits.

> NSAIDs and aspirin should be given in pregnancy only if the maternal benefits outweigh the potential fetal risks, at the lowest effective dose, and for the shortest duration possible (less than a week) with avoidance during conception and ideally after 30 weeks of pregnancy.

Paracetamol, which shares many of the indications for use with NSAIDs, had no effect on risk of miscarriage. NSAIDs and aspirin are considered to inhibit prostaglandin biosynthesis in most organ systems, whereas paracetamol inhibits its prostaglandin biosynthesis only in the central nervous system [58].

> During pregnancy the drug of choice for analgesic, anti-inflammatory, and antipyretic action is paracetamol.

Weak opioids such as codeine may be used as additional treatments to help control the pain. They are also useful if NSAIDs are not tolerated or are contraindicated as in patients with peptic ulceration. Morphine analgesia and its derivatives should be avoided, as they may cause spasm of the sphincter of Oddi. This spasm may exacerbate an already painful acute cholecystitis or biliary obstruction.

21.2.3 Thromboprophylaxis

21.2.3.1 General Recommendations

The annual frequency of deep venous thrombosis (DVT) in the general population is 0.16–1% [64, 65], of which 2% are pregnancy-related [66]. Therefore, the risk of a thromboembolic event, either DVT or pulmonary embolism (PE), during pregnancy and puerperium is estimated to be tenfold higher reaching up to 2% [64, 67–70]. Gestational hormones, particularly estrogen, contribute to a mild hypercoagulability during pregnancy by increasing the synthesis of clotting factors [71]. Thromboembolic phenomena are also promoted by intra-abdominal vascular stasis resulting from compression by the enlarged gravid uterus. The risk may, in fact, increase exponentially across the duration of the pregnancy [72]. Puerperium is the period with highest venous thromboembolism (VTE) risk, up to 25-fold higher than that in nonpregnant women [64, 68, 70, 73]. Around 43–60% of pregnancy-related PE episodes take place during puerperium [64, 67]. Approximately, 80% of thrombotic events occur in the first 3–4 weeks after delivery and is explained not only by the immobility but also by the trauma of pelvic vessels in the course of delivery leading to endothelial damage [74].

Hypercoagulability during the obstetric period is explained by many factors, including abnormalities in coagulation proteins (increased levels of factors II, V, VII, VIII, X, and XII and von Willebrand factor and decreased levels of protein S and activated protein C) and abnormalities in the fibrinolytic system (low plasma fibrinolytic activity during pregnancy, labor, and delivery) with decreased activity of tissue plasminogen activator. The most important changes occur in the levels of factor VIII and fibrinogen, each of which increases two- to threefold [75, 76].

Risk factors for thrombosis during pregnancy are listed in the Table 21.3. The most comprehensive thromboprophylaxis guidelines for the pregnant population are made by the *American College of Chest Physicians* Evidence-Based Clinical Practice Guidelines 2012 [69].

- Low-molecular-weight heparin (LMWH) is recommended for the prevention and treatment of VTE, instead of unfractionated heparin (UFH).
- For women receiving anticoagulation for the treatment of VTE who become pregnant, LMWH is recommended over vitamin K antagonists.
- The use of fondaparinux and parenteral direct thrombin inhibitors should be limited to those with severe allergic reactions to heparin (e.g., HIT) who cannot receive danaparoid.

Table 21.3 Risk factors for thrombosis during pregnancy [64, 65, 67, 68, 73]

Thrombophilic disorders	Causes related to pregnancy	General risk factors
Antithrombin deficiency	Immobility	Age >35 years
Factor V Leiden	Parity ≥3	Body mass index >30
Antiphospholipid antibodies	Multiple gestation	History of deep vein thrombosis
Hyperhomocysteinemia	Weight gain >21 kg	Smoking
Protein C deficiency		Diabetes mellitus
Homozygous MTHFR C677T	Prolonged labor >12 h	Major abdominal surgery for >30 min
Protein S deficiency	Preeclampsia	
Prothrombin gene mutation	(Emergency) cesarean section	Anemia
Plasminogen activator inhibitor-1 (PAI-1) 4G/5G	Blood loss (>1 L)/blood transfusion	Black race
	Preterm delivery	Dehydration
	Mid-cavity instrumental delivery	Infections
	Hyperemesis	Severe varicose veins
	Assisted reproductive techniques	Systemic lupus erythematosus

- Avoid the use of oral direct thrombin (e.g., dabigatran) and anti-Xa (e.g., rivaroxaban, apixaban) inhibitors.
- For lactating women using warfarin, acenocoumarol, or UFH who wish to breastfeed, continuing the use of warfarin, acenocoumarol, or UFH is recommended.
- For lactating women using LMWH, danaparoid, or r-hirudin who wish to breastfeed, continuation of LMWH, danaparoid, or r-hirudin is recommended.
- For breastfeeding women, alternative anticoagulants rather than fondaparinux are recommended.
- For breastfeeding women, alternative anticoagulants rather than oral direct thrombin (e.g., dabigatran) and factor Xa inhibitors (e.g., rivaroxaban, apixaban) are recommended.
- For lactating women using low-dose aspirin for vascular indications who wish to breastfeed, continuation of this medication is recommended.
- For women undergoing assisted reproduction, routine thrombosis prophylaxis is not recommended.
- For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome is recommended.
- For all pregnant women with prior VTE, postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0–3.0 is recommended.
- For pregnant women at low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen), only clinical vigilance antepartum is recommended.
- For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), antepartum prophylaxis with prophylactic- or intermediate-dose LMWH is recommended.
- For pregnant women receiving long-term vitamin K antagonists, adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum is recommended.
- For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history of VTE, antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0–3.0 is recommended.
- For pregnant women with all other thrombophilias and no prior VTE who have a positive family history of VTE, antepartum clinical vigilance, and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or in women who are not protein C or S deficient, vitamin K antagonists targeted at INR 2.0–3.0 are recommended.
- For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history of VTE, antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0–3.0 are recommended.
- For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, antepartum and postpartum clinical vigilance is recommended.

- For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), screening for APLAs is recommended.
- For women with a history of pregnancy complications, no screening for inherited thrombophilia is recommended.
- For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, antepartum administration of prophylactic- or intermediate-dose UFH, or prophylactic LMWH combined with low-dose aspirin, 75–100 mg/day is recommended.
- For women with inherited thrombophilia and a history of pregnancy complications, antithrombotic prophylaxis is not recommended.
- For women considered at risk for preeclampsia, low-dose aspirin throughout pregnancy, starting from the second trimester, is recommended.
- For women with two or more miscarriages but without APLA or thrombophilia, antithrombotic prophylaxis is not recommended.
- For pregnant women with mechanical heart valves: (a) adjusted-dose bid LMWH throughout pregnancy to achieve the manufacturer's peak anti-Xa LMWH 4-h post-subcutaneous injection or (b) adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval aPTT at least twice control or attain an anti-Xa heparin level of 0.35–0.70 units/mL or (c) UFH or LMWH (as above) until the 13th week, with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed.

21.2.3.2 Low-Risk Surgery

Many factors can alter postoperative coagulation. These include the type of the operation [77] and the type of the anesthesia [78]. Postoperative changes in cytokine level are affected by even more factors: the type of the procedure and the anesthetic technique or anesthetic agent [79], the duration of the operation [80], and the use of autologous or allogenic transfusion [81].

Open surgery, as compared with laparoscopic procedures, leads to activation of the clotting system of a higher degree, implying a greater thromboembolic risk for patients undergoing open surgery. Subclinical fibrinolysis was also more profound in the open surgery group. Although of a lower degree, hypercoagulability is still observed in patients undergoing laparoscopic surgery. This fact, combined with the pneumoperitoneum-induced venous stasis of the legs, explains the reduced, but not negligible, rate of thromboembolic complications after laparoscopic surgery. Therefore, routine thromboembolic prophylaxis (subcutaneous LMWH, elastic compression stockings, intraoperative pneumatic stockings, and early postoperative patient mobilization) should be considered for patients undergoing laparoscopic surgery [82]. Gestational hormones, particularly estrogen, contribute to a mild hypercoagulopathy during pregnancy by increasing the synthesis of clotting factors [71]. If a laparotomy can be avoided, recovery time is greatly reduced; thus, postoperative complications due to immobilization, such as DVT and PE, are less likely. Prophylaxis with pneumatic compression devices both intraoperatively and postoperatively and early postoperative ambulation are recommended as in the nonpregnant patients.

Low-risk groups include appendectomy via laparoscopy or gridiron incision, isolated Fallopian tube torsion, and (ruptured) ectopic pregnancy. There are no recommendations for thromboprophylaxis after emergency laparotomy or laparoscopy in pregnancy; therefore, similar recommendations should apply as for the general pregnant patients after these operations. The use of calf length sequential pneumatic compression stockings not only increases venous return but also prevents the risk of VTE [83]. Early ambulation further minimizes or eliminates the VTE risk.

21.2.3.3 Elective Cholecystectomy

A marked hypercoagulable state after LC is seen by an increase in the thromboelastographic index, on the first postoperative day compared with preoperative values [77]. Reports have documented a reduction in postoperative hypercoagulability after laparoscopic cholecystectomy (LC) compared to open cholecystectomy (OC) [84, 85]. A significant increase in prothrombin fragment F1+2 levels after LC is found, but these levels were significantly lower than after OC [85]. Conversely, others have not found the difference in postoperative hemostasis between LC and OC [86, 87], and fibrinogen levels increased and reached maximum levels at 72 h, but significantly less after LC than after OC, while plasminogen levels decreased postoperatively without a significant difference between groups [88]. Laparoscopic surgery is associated with a lesser degree of thromboembolic complications despite pneumoperitoneum which, by reducing venous inflow toward the heart, promotes venous stasis of the legs and predisposes to DVT [89, 90]. TAT, F1, FIB, soluble fibrin, and D-dimer plasma levels until 72 h after surgery were significantly higher in the OC group than in the LC group, implying significantly higher activation of coagulation and fibrinolysis in the OC group [88]. The levels of coagulation factors and cytokines were in average two times higher in OC group. Other nonrandomized studies found insignificant differences of fibrinolytic activity between OC and LC groups [86, 87, 91].

21.2.3.4 Emergent Cholecystectomy

Current data show that emergent LC carry better fetal prognosis that delayed cholecystectomy (see Sect. 2.1.9.1). Still, there are several issues unresolved. First is coagulation and fibrinolysis mechanisms during pregnancy complicated with acute cholecystitis. Second is the question of coagulation during the complete process of cholecystitis as a disease. Is it better to perform emergent cholecystectomy with initially increased coagulation or to start medical management which, due to inflammation, also increases coagulation? And then coagulation is also increased in the second phase of the treatment process when delayed elective cholecystectomy is performed. There are no recommendations for additional thromboprophylaxis in acute cholecystitis during pregnancy.

IVF Pregnancy

Currently, there is only one case report of LC due to acute cholecystitis during pregnancy [71]. Thromboprophylaxis should be recommended in dosage for IVF pregnancy itself due to its higher risk for VTE. Prospective studies should solve this issue.

21.2.3.5 General IBD Patients

IBD patients in general, particularly hospitalized with the active disease, are at increased risk for VTE [92, 93]. Hospitalized pregnant IBD patients have an increased risk of VTE compared to their non-IBD pregnant controls, for CD an OR 6.12 and for UC an OR 8.44. LMWH in a prophylactic dose reduces the risk of VTE in medical and surgical patients by 60–70%.

LMWH has been shown to be safe and efficacious in the pregnant population [94]. Therefore, consideration of the use of prophylactic LMWH in pregnant IBD patients experiencing a relapse and/or admitted to hospital is recommended (ECCO Consensus). All women should undergo a documented assessment of risk factors for VTE in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to hospital for any reason and again after delivery.

21.2.3.6 Cesarean Section

The VTE incidence rate following CS is 1.78%, with an odds ratio of 2 [67]. Thromboprophylaxis guidelines from *American College of Chest Physicians* Evidence-Based Clinical Practice Guidelines 2012 for women undergoing CS are presented [69]:

- For women undergoing CS without additional thrombosis risk factors, thromboprophylaxis is not recommended other than early mobilization.
- For women at increased risk of VTE after CS because of the presence of one major or at least two minor risk factors, pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in hospital following delivery is recommended.
- For women undergoing CS who are considered to be at very high risk for VTE and who have multiple additional risk factors for thromboembolism that persist in the puerperium, prophylactic LMWH should be combined with elastic stockings and/or intermittent pneumatic compression.
- For selected high-risk patients in whom significant risk factors persist following delivery, extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital is recommended.

21.2.3.7 Torsion of the Gravid Uterus

Several cases of PE after uterine detorsion [95, 96] were described of this extremely rare entity. Therefore, LMWH (enoxaparin 20 mg once a day) for 6 weeks to prevent VTE is recommended [97].

21.2.3.8 Venous Thromboembolism

Therapeutic recommendations for VTE during pregnancy from the *American College of Chest Physicians* Evidence-Based Clinical Practice Guidelines 2012 are presented [69]:

- For pregnant women with acute VTE, adjusted-dose subcutaneous LMWH over adjusted-dose UFH is recommended.
- For pregnant women with acute VTE, LMWH over vitamin K antagonist treatment antenatally is recommended.
- For pregnant women with acute VTE, anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months).
- For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, discontinuation of LMWH at least 24 h prior to induction of labor or CS (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery is recommended.

21.3 Perioperative Management

21.3.1 Fetal Heart Rate Monitoring

There are two principal types of fetal heart rate monitoring: internal and external (Fig. 21.2). When emergency abdominal conditions are considered only external type is used. Fetal heart rate after 16 weeks of pregnancy should be monitored pre- and postoperatively in the setting of urgent abdominal surgery during pregnancy (Evidence level III) [33, 34]. While intraoperative fetal heart rate monitoring (every 5 min in the lower left quadrant without disinflation) was once thought to be the most accurate method (Fig. 21.3) to detect fetal distress during laparoscopy, no intraoperative fetal heart rate abnormalities have been reported [98, 99]. External monitors of uterine contractions are variably effective in the insufflated abdomen [100].

The effects of general anesthesia on cardiotocography result in a reduction of beat-to-beat variation with normal baseline frequency. The decreased variability can persist until 90 min in the postoperative course due to the residual effects of anesthetic agents on the fetus. This could be misinterpreted as fetal distress leading to emergency delivery and hence added to fetal morbidity and mortality [103]. An additional factor that can influence intraoperative beat-to-beat variations is surgical manipulation, especially of the pregnant uterus, primary inflammatory process or hemorrhage, and preoperative anxiety and stress which can increase the levels of catecholamines further. Transvaginal sonography should be used during the procedure

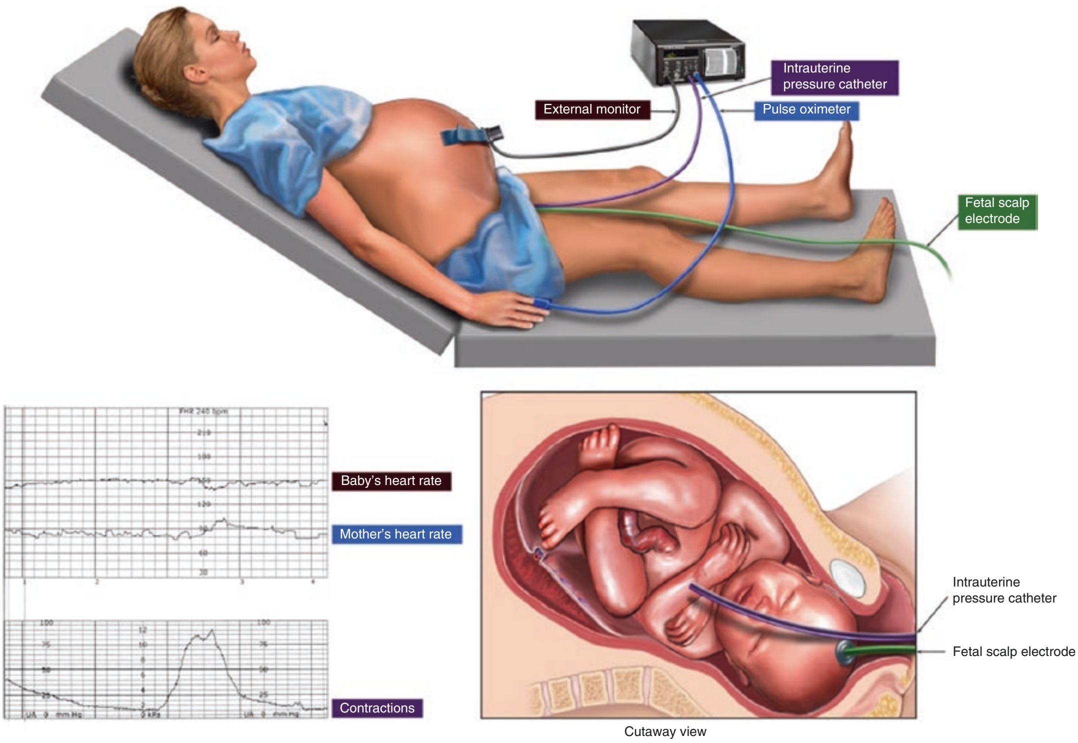

Fig. 21.2 Internal and external type of fetal heart rate monitoring (Reproduced from the webpage [103] permission for publication)

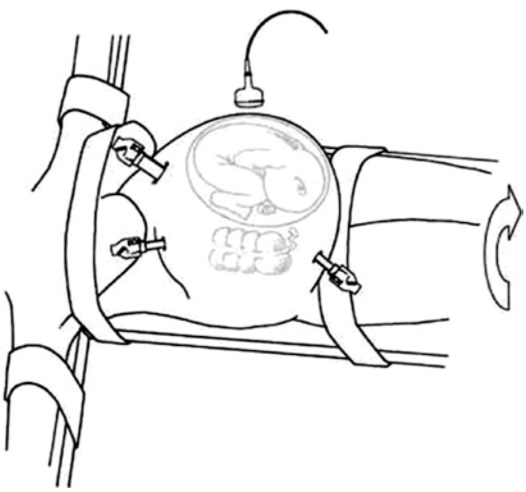

Fig. 21.3 Patient positioning, port placement, and intraoperative fetal monitoring in advanced pregnancy (Reproduced from [104] under the CC BY 3.0)

because the signals from transabdominal ultrasound would be lost during insufflation [104–106]. This has led some to recommend the only pre- and postoperative monitoring of the fetal heart rate as no increased fetal morbidity has been reported [33, 34].

Special monitoring precautions beyond those usually employed during general anesthesia—continuous maternal pulse oximetry, end-tidal CO_2, monitoring, electrocardiography, and pulse rate measurements, combined with frequent blood pressure measurements—have generally not been employed. In addition, in women predisposed to significant hypercarbia, changes in end-tidal CO_2 may lag significantly behind maternal $PaCO_2$. Frequent direct measurements of maternal $PaCO_2$ via an arterial catheter may be warranted [106].

Some faults of pneumoperitoneum can be avoided with the use of gasless laparoscopy. There are fewer derangements in maternal and fetal physiology without the use of CO_2 pneumoperitoneum. Moreover, it is possible to perform the surgical procedures under locoregional (peridural or spinal) rather than general anesthesia.

21.3.2 Nutrition and Dietary Supplements

21.3.2.1 Total Parenteral Nutrition and Refeeding Syndrome

See Sect 7.1.5.1.

21.3.2.2 Perinatal Outcome

Symptomatic cholelithiasis and/or cholecystitis in pregnant women could be associated with a higher risk of neural tube defects in the offspring [107]. Due to a small sample, confounding factors, all that can cause preterm labor should be considered. Previous studies indicated an association between neural tube defects or other congenital anomalies and high fever during the critical period [108]. Some pregnant women with symptomatic cholelithiasis and/or cholecystitis reported fever. Currently, there are no data regarding the possible association between the bacterial causes of cholecystitis and neural tube defects [109]. The drugs used for the treatment of symptomatic cholelithiasis and/or cholecystitis have no role in the origin of neural tube defects. The use of folic acid and folic acid-containing multivitamins was less frequent in symptomatic cholelithiasis and/or cholecystitis group partly due to a higher rate of anorexia or episodes of vomiting. The hypothesis for the explanation of the possible association between symptomatic cholelithiasis and/or cholecystitis and neural tube defects is based on the observation that this condition frequently includes fever which, per se, may have a role in the origin of neural tube defects (see Sect. 23.7.3). Thus, periconceptional folic acid/multivitamin supplementation in pregnant women with symptomatic cholelithiasis and/or cholecystitis is recommended [107, 108] and probably other abdominal conditions when the caloric intake is diminished.

Dietary supplementation of ω-3 has been suggested as secondary prophylaxis of all-cause spontaneous preterm delivery, suggesting that ω-3 fatty acids are capable of prolonging the duration of gestation in the range of 4–7 days and that dietary intake is marginal in Western populations [110]. There is a dose–response relation reflecting an intake of up to 0.15 g ω-3 fatty acids [111].

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Increased Intra-Abdominal Pressure

22

Abstract

Clinicians are often unfamiliar with maternal-fetal physiology in critical illness including the possible impact of increased intra-abdominal pressure (IAP) and intra-abdominal hypertension (IAH) on both the mother and the fetus. Pregnancy is a particular condition where multiple factors such as obesity, pre-eclampsia, or postpartum hemorrhage may lead to the over-diagnosis of abdominal compartment syndrome (ACS). When raised IAP is detected and treated, ACS may often be avoided, especially with the adoption of newer resuscitation strategies. Critical illness in pregnancy is not uncommon, given that the population-based incidence of severe obstetric morbidity has been reported to be as high as 1.2% in the UK and 1–3% in the USA. There is little data regarding physiologic and pathophysiologic IAP in pregnancy. Current consensus guidelines group pregnancy and morbid obesity together as chronically compensated states of IAH. Both operative and non-operative conditions can cause increased IAP. Despite the limited understanding of IAH in maternal care, even less is known regarding its effects on the fetus. Whether there are subclinical effects of even modest elevations of maternal IAP on the fetus is completely unknown. Therefore, in all critically ill pregnant patients, IAP should be measured. Treatment options, including non-operative and operative strategies, for its normalization, should be carried out immediately after verification of increased IAP in pregnancy.

22.1 Intra-Abdominal Hypertension

22.1.1 Introduction

Despite the World Health Organization's Millennium Development Goals that include improving maternal health worldwide by 2015, the reality remains that over one-half million expectant or new mothers die suddenly and unpredictably [1]. Although 90% of these deaths occur in developing countries, intensivists in developed countries are also confronted by unexpected critical illnesses in pregnancy, often in otherwise previously healthy women. These illnesses, most commonly preeclampsia and obstetric hemorrhage, can result in significant morbidity and mortality in both mother and newborn [2, 3]. Further complicating the situation,

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_22

intensivists are often unfamiliar with maternal–fetal physiology both in health and in critical illness including the possible impact of intra-abdominal pressure (IAP) and intra-abdominal hypertension (IAH) on such conditions [2]. Pregnancy is a particular condition where multiple factors such as obesity, pre-eclampsia, or postpartum hemorrhage may lead to the overdiagnosis of abdominal compartment syndrome (ACS). When raised IAP is detected and treated, ACS may often be avoided, especially with the adoption of newer resuscitation strategies [4, 5]. However, despite seminal work in 1913, by an obstetrician, Paramore, Hunterian Professor of the Royal College of Surgeons of England [6], there has been almost no recognition or appreciation of the potential presence, influence, and management of IAH in pregnancy and the peripartum state, other than dramatic case reports [7–9]. Critical illness in pregnancy is not uncommon, given that the population-based incidence of severe obstetric morbidity has been reported to be as high as 1.2% in the United Kingdom [10] and 1–3% in the United States [3]. Maternal hypertension and hemorrhage were the most cited causes of critical care admission [3].

22.1.2 The Physiology of Normal Pregnancy

The maternal physiologic changes during pregnancy are multisystemic due to the adaptation to accommodate the gravid uterus. On average, the uterus contributes 1 kg to the overall weight gain in pregnancy, while the amniotic fluid, fetus, and placenta comprise approximately 5 kg in additional weight [11]. To accommodate this growth, the thoracic cage increases in both anteroposterior and transverse diameters [11]. The hormone relaxin, released by the corpus luteum and placenta, results in targeted softening of the ligamentous structures to also compensate for uterine growth [12]. The diaphragm becomes elevated as a result of being pushed cephalad by the uterus, impeding the functional residual capacity by at least 20% [11]. Tidal volume increases and is associated with a 45% increase in a minute and alveolar ventilation [11]. Overall maternal metabolic rate, oxygen consumption (VO_2), gas exchange, and acid–base balance are all affected by several factors including the growth of the fetoplacental unit, progesterone levels, and CO_2 production.

On average, maternal VO_2 increases by 15–20% [13]. With increased ventilation, the resulting respiratory alkalosis is renally compensated through a reduction of serum bicarbonate to 20 mEq/L and total buffer base capacity to 5 mEq/L [11]. Thus, when critically ill, the parturient is more vulnerable to hypoxemia and acidemia, with overall less physiologic reserve, then when nonpregnant [13]. In addition, there is a 50% increase in plasma volume resulting in dilutional anemia and an overall increase in circulating blood volume of 40% [11, 13]. Cardiac output increases by 30–50%; blood flow to the gravid uterus increases tenfold [13]. After 20 weeks of gestation, the uterus size can cause a mechanical aortocaval obstruction while fully supine and can result in the "supine hypotensive syndrome": significant loss of venous return for which the cardiovascular system cannot compensate [11]. However, the majority of women develop collateral circulation through interosseous vertebral, paravertebral, epidural, and ovarian venous systems [11]. It has been suggested that those who suffer from supine hypotensive syndrome likely do not develop adequate collateral circulation [14]. While only approximately 8% of women at term experience this life-threatening situation, significant compression of the inferior vena cava while supine does occur in the majority of women [11, 14]. Whether elevated IAP can exacerbate aortocaval compression and has a relationship with this syndrome is unknown. Thus, due to the myriad of hormonal, mechano-physiologic changes, the majority of parturients are well compensated for the exponential growth of their fetus in a relatively short duration of time.

22.1.3 Intra-Abdominal Pressure in Normal Pregnancy

There is little data regarding physiologic and pathophysiologic IAP in pregnancy. Current consensus guidelines group pregnancy and morbid obesity together as chronically compensated states of IAH [15]. Unlike pregnancy, chronic obesity is the deposition of fat diffusely throughout the abdominal cavity. The implication of this anatomical difference could be considered semantic by some, but could be considered significant, given that the standard of measurement of IAP uses the intravesical pressure as a surrogate, the location of which rests in the pelvis. First evidence concerning IAP in pregnancy was obtained through rectal manometry in 1913 [6]. Recently, intravesical measurements in healthy term parturients obtained under spinal anesthesia just prior to the commencement of elective Cesarean section (CS) found the median IAP in a leftward tilted position to be 22 ± 2.9 mmHg (range 15–29 mmHg) [16]. These IAP values are actually in the threshold range for ACS if organ failure were also present [15]. However, the methodology could have created some bias leading to an overestimation of IAP values. Dermatome level of spinal anesthetic was unknown leading to possible under relaxed abdominal wall muscle, and 50 mL instead of 25 mL was instilled in the bladder for the measure. Postoperatively, after neonatal delivery, the IAP dropped significantly to a median IAP of 16 mmHg (range 11–24 mmHg) [16]. Besides previous questions, the greatest question is the unspecified degree of left lateral tilt during the IAP measurements, making it difficult to reconcile if these measurements reflected the actual abdominal IAP or the weight of the gravid uterus on the bladder itself. There is debate as to the degree of tilt required to minimize compression of the IVC by the uterus [17, 18]. Another study on term parturients under spinal anesthesia showed significantly higher IAP in the supine position compared to left lateral tilt of 10° with the reference point held constant by placing the bladder pressure transducer in a line adjacent to the patient on an intravenous pole [19]. The weight of the gravid uterus might have directly impacted on the bladder, thereby falsely elevating the IAP measurement when fully supine. Also, there is a concern regarding the positioning of ventilated patients fully supine to measure IAP while increasing aspiration risks [20–22].

> Left lateral tilt has become the standard of care in CS, particularly after spinal anesthesia, as a means to both facilitate CS and alleviate potential aortocaval compression while supine [17]. A tilt of 15° is generally recommended [17].

What remains unknown is the effect of the gravid uterus on measured bladder pressure in varying relative positions to each other. Questions arise as to the validity of the IAP measurement as recommended by the *World Society of the Abdominal Compartment Syndrome* guidelines in a pregnant patient from early second trimester onward. Current recommended guidelines describe IAP measurement in the fully supine position at end-expiration [23, 24]. Such a maneuver in pregnancy, however, could be detrimental. It is known that lateral tilt does not provide fetal/neonatal benefits in Apgar scores or umbilical-artery pH and is therefore not mandatory [25, 26]. Therefore, term pregnancy is associated with elevated IAP to which the patient has adapted. The IAP is elevated in the immediate postpartum period [16, 27], similar to the postoperative surgical populations [28].

Paramore published the only serial IAP readings throughout the pregnancy and postpartum. Measurements were obtained rectally, and data were extracted for the standing, supine, left lateral, and knee–chest positions [6]. The highest IAP mean value was obtained in the standing position, and the lowest positive IAP mean value was obtained in the left lateral. The knee–chest position (inversion of the abdominal orientation) produced a negative-pressure mean value (Fig. 22.1). The question about precise results could be the question whether the probes inserted in the lower abdomen (rectum, bladder) could produce more IAP increase in the lower than in the upper abdomen.

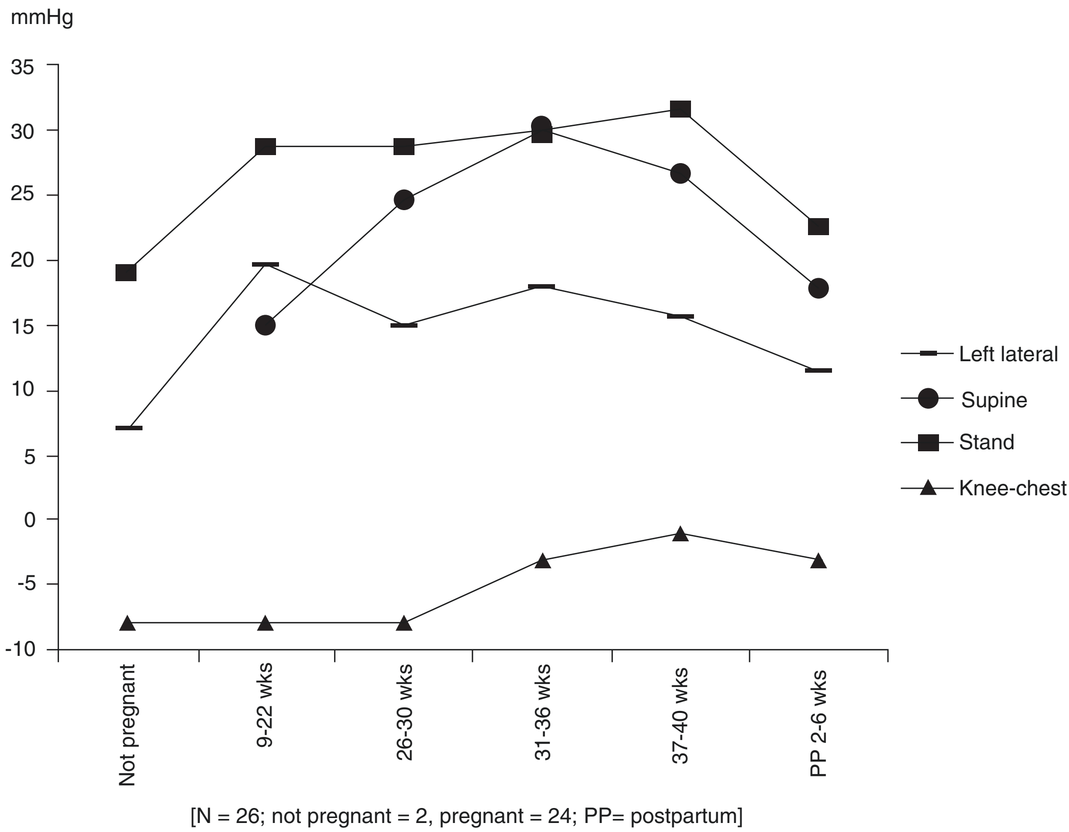


Fig. 22.1 Mean intra-abdominal pressure by position and gestational age. Reproduced with permission from [29]

22.1.4 Pathophysiology of IAH/ACS

22.1.4.1 Physical Laws and IAP in Pregnancy

The relationship between IAP and pregnancy is defined by the equation DIAP = DIAV/Cab (change in IAP = change in intra-abdominal volume/abdominal compliance) [30]. This equation considers the magnitude or volume of the abdomen in the supine position, which is appropriate for critically ill patients [30]. Abdominal compliance or elasticity is calculated by a change in volume divided by change in pressure (L/mmHg) and describes tolerance to increases in intra-abdominal volume [30]. However, pregnant women are mobile, and IAP in pregnancy varies with position [6, 16, 19, 27, 31]. Therefore, the equation is expanded to incorporate the unique vector dynamics of the maternal abdomen, as vector force more accurately describes both volume magnitude and force direction (consideration of weight due to gravity): VF = VM + D (vector force = volume magnitude + direction) [30, 32]. Hence, applied to pregnancy, the formula is DIAP-P = DIAVF/Cab (change in IAP in pregnancy = change in abdominal vector force (volume + direction)/abdominal compliance.

The formula DIAP = DIAV/Cab assumes a curvilinear relationship between abdominal volume and pressure that is dependent on abdominal wall compliance [30]. Following the initial linear slope, an exponential increase in pressure occurs once the critical volume is attained. This formula and curvilinear relationship reflect the principle of Laplace's law, which addresses the relationship between radius (volume), pressure, and wall tension [32]. The greater the radius (volume), the greater a wall tension is required to withstand internal fluid pressure. Based on these principles, and at constant atmospheric pressure, the formula

DIAP-P = DIAVF/Cab assumes a similar curvilinear relationship between abdominal vector force and IAP-P that is dependent on abdominal wall compliance.

22.1.4.2 Digestive System Pathophysiology

IAH/ACS results in hemodynamic shifts, including decreased venous, arterial, and microcirculatory flow and increased systemic resistance resulting in ischemia reperfusion injury [30]. This compromised microcirculatory flow and oxidative stress cause epithelial damage and disruption of the mucosal integrity in the intestinal epithelium, leading to intestinal permeability [33, 34]. Epithelial integrity is further compromised with the loss of intercellular tight junction integrity and loss of intestinal barrier function [35]. This leads to translocation of LPS endotoxin from gram-negative bacteria to the mesenteric lymph nodes, the portal vein, and the liver [33, 34]. The exposure of Kupffer cells to LPS endotoxin initiates a cytotoxic immune response. Multiple proinflammatory cytokines mediate the endotoxic effects of LPS in the systemic circulation; this results in a systemic inflammatory response, oxidative stress, and subsequent multiorgan failure [36, 37]. The evidence demonstrates that the LPS response is mediated by the liver, while the immune response characteristic of preeclampsia is mediated by the placenta.

In addition to intestinal ischemia reperfusion injury causing mucosal epithelial injury, the loss of barrier function may be caused by two environmental factors: abnormal exposure to enteric and pathogenic bacteria and small intestine exposure to dietary gliadin [38, 39]. Therefore, intestinal permeability is caused by (1) intestinal ischemia reperfusion injury, (2) exposure to enteric pathogenic bacteria, and (3) exposure to dietary gliadin.

22.1.4.3 IAH/ACS and the Fetus

Despite the limited understanding of IAH in maternal care, even less is known regarding its effects on the fetus. Whether there are subclinical effects of even modest elevations of maternal IAP on the fetus is completely unknown. Animal studies have confirmed that the mammalian fetus in utero is subject to transmitted IAP [40]. IAH decreases uterine blood flow and induces a resultant compensatory fetal hypertension [41] such as during laparoscopy even with inert gases rather than CO_2. In a 20-day gravid rabbit model, an intraperitoneal air was insufflated to an IAP of 20 cmH_2O. IAMNP was linearly related to IAP as defined by IAMNP = IAP × 0.8 + 2.0. Further, the elevation of IAMNP to 15.6 cmH_2O via the elevation of the IAP (to 17 cm H_2O) altered the contractile properties of the fetal bladder [40]. While there are no recent human data correlating maternal IAH with any known effects on the fetus, concerns regarding the fetoplacental unit are neither entirely novel nor implausible. One hypothesis is that elevated IAMNP is translated to elevated fetal IAP, both of which were vulnerable to elevations in maternal IAP [42]. Through this mechanism, elevated fetal IAP could result in increased urethral resistance, the chronicity of which could lead to abnormal development of the bladder detrusor muscles, resultant dysfunctional voiding in children, and possible urinary tract anomalies [42]. Although the etiology of such syndromes is likely multifactorial, exploration of the impact of pathological maternal IAH on the fetoplacental unit could be another area of potential investigation. Ovarian hyperstimulation syndrome (OHSS) is a not an uncommon complication of ovulation induction for assisted reproduction [43, 44]. The mechanism is not entirely understood but is thought to be mediated by vasoactive cytokines in response to exogenous administration of human chorionic gonadotropin [45]. Significant third spacing as a result of capillary vascularity due to ovarian neoangiogenesis can occur [43], and in its most severe form, massive and rapid accumulation of abdominal ascites results in an overt ACS [45].

In addition to increased IAP, pregnant rats exposed to LPS had higher serum TNF-α levels, and TNF-α-mediated inflammation resulted in [46, 47] (1) deficient trophoblastic invasion and spiral artery remodeling; (2) altered uteroplacental hemodynamics and increased average spiral artery resistance index; (3) placental nitrosative stress; (4) increased maternal mean arterial pressure; (5) maternal renal structural alterations, including mesangial hypercellularity and occlusion of

capillary loops; (6) significant maternal elevation of protein/creatinine ratios and proteinuria; (7) fetal death in a dose-dependent manner within 3–4 h of LPS exposure; (8) fetal growth restriction in the surviving fetuses; and (9) maternal coagulopathy in cases of fetal death.

22.2 Etiopathogenesis

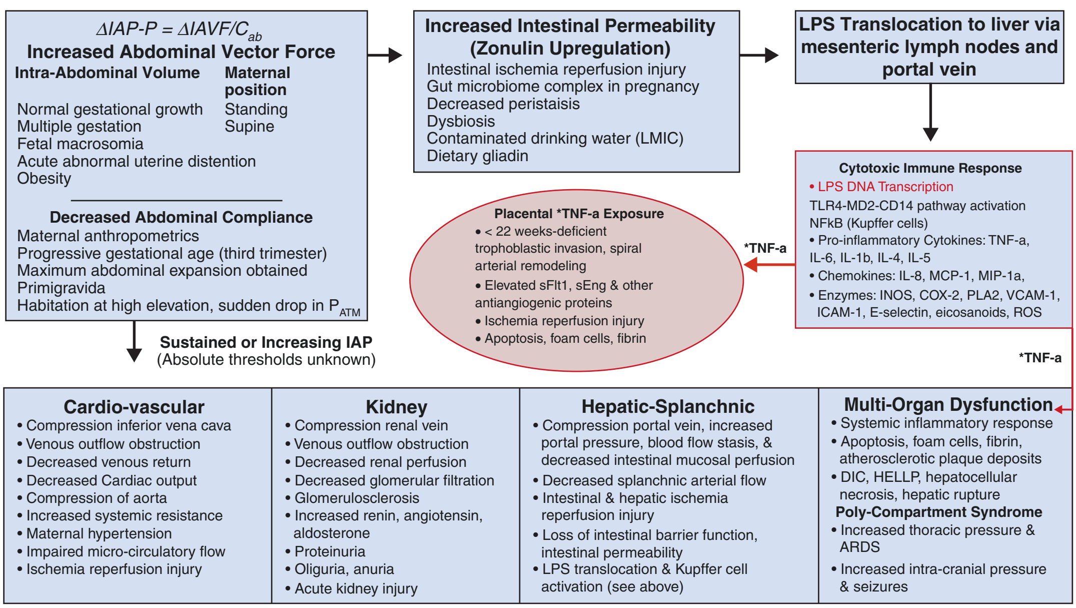
IAH/ACS in pregnancy presumes a causal pathway, which may be intrinsically and/or environmentally triggered (Fig. 22.2). This hypothesis includes the relationship of independent and dependent variables, the temporal-spatial positioning of etiological factors, and the role of genetic factors.

22.2.1 Nonoperative Conditions

22.2.1.1 Preeclampsia

François Mauriceau (Fig. 22.3) noted the preponderance of "toxemia" of pregnancy in primiparas in 1694 [48]. Even as early as the 1900s, Paramore had suggested uncompensated elevated IAP as a possible etiologic factor in the development of preeclampsia [6, 49]. Paramore also hypothesized that nulliparous and muscular women were prone to spastic abdominal wall tone resulting in elevated IAPs, compromising perfusion pressure to the abdominopelvic viscera [6, 49]. Mulier was able to indeed confirm a linear relationship between IAP and volume to calculate the abdominal wall elastance [50] and even found that it decreased significantly with increased age and gravidity [51].

Preeclampsia is part of a spectrum of hypertensive disorders of pregnancy, defined as the presence of arterial hypertension (blood pressure BP ≥140/90 mmHg) on two occasions, at least 6 h apart, but without evidence of end-organ damage, of a woman who was normotensive before 20 weeks of gestation and proteinuria (>0.3 g/24 h). In a patient with preexisting essential hypertension, preeclampsia is diagnosed if systolic BP has increased by 30 mmHg or if diastolic BP has increased by 15 mmHg [53].



ARDS = Acute respiratory distress syndrome; CD14 = cluster of differentiation14; COX-2 = cyclooxygenase 2; DIC - disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzymes, low platelets; IAP - intra-abdominal pressure; ICAM-1 = intercellular adhesion molecule-1; iNOS = inducible nitric oxide synthase; LMIC = low & middle income countries; LPS = lipopolysaccharide; PATM = atmospheric pressure; MCP-1 = monocyte chemotactic protein-1; MD2 = myeloid differentiation co-receptor 2; MIP-1a = macrophage inflammatory protein-1a; NFkB - nuclear factor kappa-light-chain-enhancer of activated B cells; PLA2 = phospholipase 2; ROS = reactive oxygen species; sEng = soluble endoglin; sFlt1 = soluble fms-like tyrosine kinase-1; TLR4 = tolHike receptor 4; TNF-a = tumor necrosis factor a; IL = interleukins; VCAM-1 = vascular cell adhesion molecule-1.
*TNF-a = TNF-a plus other proinflammatory cytokines, chemokines and enzymes
IAP-P = IAVF/ C_{ab} [Change in intra-abdominal pressure in pregnancy = change in abdominal vector force (volume + direction)/abdominal compliance]

Fig. 22.2 Intra-abdominal hypertension in pregnancy etiology pathway. Reproduced with permission from [29]

Fig. 22.3 François Mauriceau (Paris 1637–Paris 1709) received his training in obstetrics at the *Hôtel-Dieu*. He was a leading obstetrician in seventeenth-century Europe – in 1668 he published, *Traité des Maladies des Femmes Grosses et Accouchées*, a book that helped establish obstetrics as a science (Reproduced from [52])

Preeclampsia is caused by IAP in pregnancy ≥12 mmHg, which when sustained or increasing, leads to hemodynamic shifts, intestinal ischemia reperfusion injury, translocation of lipopolysaccharide endotoxin to the liver, systemic cytotoxic immune response, multi-organ dysfunction, and poly-compartment syndrome [29].

Some of these clinical manifestations have been well described as early as the mid-1600s [48], but etiology remains incomplete. The most commonly held hypothesis is that abnormal placentation occurs during the myometrial trophoblastic invasion in the second trimester [53], leading to placental ischemia and the release of angiogenic toxins, causing widespread endothelial dysfunction [54] and generalized inflammation. However, this immune maladaptation hypothesis has been questioned [55]. While its incidence worldwide is significant (3–5% of all pregnancies) [53], preeclampsia is a heterogeneous condition for which its commoner presentation in younger women in developing countries may be etiologically distinct than that of the somewhat older preeclamptic presentation in developed nations, with clinically [20] milder disease occurring later in gestation [55]. Furthermore, ACS is widely unrecognized because the routine measurement of IAP generally has not been accepted in many ICUs. Akin to many other conditions in critical illness, clinicians too frequently do not consider the possible impact of IAH in the clinical picture, especially when the patient has not been injured or subjected to surgery [56, 57].

The endothelial dysfunction leads to increased vascular permeability in addition to possible hypoalbuminemia, which in turn causes third spacing of fluids resulting in significant intra-abdominal fluid collections. The fluid extravasation causes relative intravascular depletion which may cause decreased urine output. Immediate postpartum IAPs are higher than in the normal postoperative population [27] that is more prominent in pregnancies complicated with arterial hypertensive disorders of pregnancy/HELLP. The combination of higher IAPs and abnormal renal function may falsely lead the physician to the diagnosis of ACS. This may, in turn, lead to unnecessarily aggressive management options. Therefore if proteinuria is present with IAP/IAH, preeclampsia should be ruled out (proteinuria after the 20th week of gestation).

IAH play a central role in initiating the multisystem cascade of diminished perfusion and inflammation associated with the various clinical manifestations of preeclampsia [58]. Obstructed venous return from IAH, essentially limiting abdominal perfusion pressure due to increased back pressure, results in decreased end-organ perfusion including both kidneys and the placenta. Thus, the activation of the renin–angiotensin system, with an elevation of aldosterone levels, systemic hypertension, and placental ischemia/necrosis with an impact on fetal growth, is triggered [58].

What remains to be seen is whether preeclamptic patients truly have IAH, at what pressure does this occur, and whether IAH has a

significant role in the progression of the development of severe preeclampsia or HELLP.

22.2.1.2 HELLP Syndrome

HELLP is considered a severe variant of preeclampsia and manifests as a syndrome of hemolysis, elevated liver enzymes, and low platelet count [54]. Due to hormonal influences during pregnancy, the abdominal wall is slowly stretched, increasing its compliance, which reduces the potential for an increase in IAP caused by the expanding uterus. Spontaneous rupture of a hepatic subcapsular hematoma (see Sect. 11.3) results in intra-abdominal hemorrhage, a well-recognized though rare complication of HELLP syndrome. Continued intraperitoneal hemorrhage and fluid resuscitation can ultimately lead to the development of IAH and ACS along with hemorrhagic shock [9].

22.2.1.3 Ovarian Hyperstimulation Syndrome

Grossman et al. published the most comprehensive review of OHSS and ACS [59]. Vascular endothelial growth factor increases VP, and transcapillary fluid dynamics studies in OHSS patients confirmed a reduction in the colloid osmotic gradient favoring leakage to the extravascular space [60]. This "third spacing" leads to depletion of the intravascular volume, ultimately resulting in hypotension. Because hypotension leads to decreased venous pressure and reduced venous return, a decreased cardiac output might be expected; however, studies have found the cardiac output increased in OHSS, while mean arterial pressure and peripheral vascular resistance decreased [61]. These findings led to the determination that there is accompanying arterial vasodilation in OHSS [62]. The hypotension also affects organ function because of the decreased perfusion. Reduced perfusion of the kidney leads to a decreased glomerular filtration rate and can result in oliguria. When transvaginal oocyte retrieval is used, the component of inoculation of the infection of ascitic fluid can be present [63]. Undiagnosed diabetes mellitus and hypothyroidism can lead to persistent OHSS hyperstimulation and pelvic infection [64].

22.2.1.4 Obesity

Baseline IAP is approximately 9–14 mmHg higher in morbidly obese patients than the baseline [20, 27]. Increased BMI and previous abdominal surgery increase mean IAP [28].

22.2.1.5 Obstetric/Gynecologic Conditions

A pathological increase in intra-abdominal volume is seen with multiple gestations, fetal macrosomia, polyhydramnios, fetoplacental hydrops, and large hydatidiform moles [65, 66].

Like OHSS, rapid growth in abdominal girth, dyspnea, abdominal pain, and other overt symptoms of ACS in other gynecologic conditions must also be considered in the differential. Patients undergoing ovulation induction are also at increased risk of ovarian torsion and ectopic pregnancy [44]. Meigs' syndrome, solid ovarian tumors associated with hydrothorax and ascites, has been described similarly to OHSS in presenting with symptoms of ACS [67].

22.2.2 Operative Conditions

Normal postoperative pressures following abdominal surgery range between 3 and 15 mmHg in general population [68]. There has been a paucity of information with regard to IAP in an entirely female and obstetric population.

22.2.2.1 Cesarean Section

The Centers for Disease Control and Prevention's National Center for Health Statistics reported that the CS rate in 2004 reached an all-time high of 31.3% [69]. Given this, and as the complexity of repeat CS increases, the establishment of normal IAP is timely and necessary. IAP in an uncomplicated pregnancy undergoing elective CS at term is significantly higher in the preoperative period (14.2 mmHg) and then recovers rapidly in the postoperative period to a level (11.2 mmHg) that sustained for 2 h (10.7 mmHg) but at an elevated level [31]. Obese patients (BMI >30 kg/m^2) have

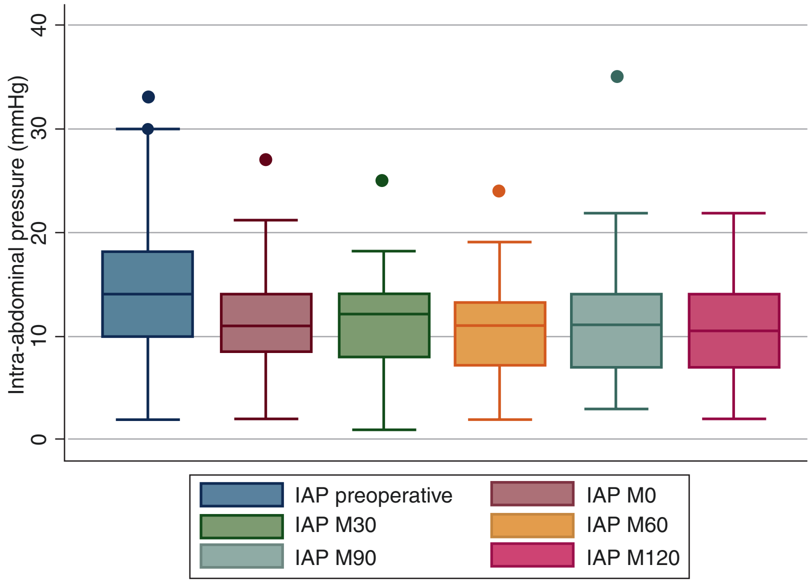


Fig. 22.4 Intra-abdominal pressure before Cesarean section (preoperative) and postoperative (every 30 min during 2 h) (Reproduced from [31] under the CC Attribution License)

significantly higher preoperative IAP levels than nonobese patients, 15.7 mmHg vs. 12.4 mmHg, respectively (Fig. 22.4). However, this difference disappears after delivery [31]. However, this value is in accordance with the standard value of IAP following uncomplicated abdominal surgery (10–15 mmHg) [68, 70]. Many factors have been described to explain this physiological increase after surgery, but in obstetrics, the two main etiologies are probably the persistent increase in uterine size and the CS itself.

> Every pregnant woman admitted to ICU after delivery should be monitored for IAP.

22.2.2.2 Laparoscopic Pneumoperitoneum

Despite the conventional dogma that the first and third trimesters are higher-risk periods for laparoscopy, there have been no reported fetal deaths after laparoscopic cholecystectomy in either of these trimesters. The use of elective laparoscopy in the first trimester of pregnancy is controversial [71] because of the unknown effects of the CO_2 pneumoperitoneum on the developing fetus [72, 73].

> There is no increased risk for obstetric outcomes with elective laparoscopy [74, 75], while the greater fetal loss in emergency surgery is attributed to intraperitoneal inflammation or hemorrhage but without changes in obstetric outcomes between open and laparoscopic approach [76].

Limited data exist concerning fetal–maternal interactions during laparoscopy. As a general principle, when the fetal–maternal unit is stressed, the mother is “conserved” at the expense of the fetus. For example, the normally decreased maternal $PaCO_2$ during pregnancy may be important in assuring adequate transplacental CO_2 diffusion from the fetus to the mother for subsequent pulmonary excretion. CO_2 pneumoperitoneum may cause maternal and subsequent fetal hypercarbia, due to decreased maternal ventilation and increased transperitoneal CO_2 absorption by the mother. Experiments on pregnant sheep with CO_2 pneumoperitoneum of 15 mmHg showed a drop in pH into acidemic range both in the mother and parallel to it in the fetus [72]. After 30 min a steady state is reached. Hyperventilating the mother brings the pH of both back to normal ranges. There were no changes in PaO_2. There

also were some hemodynamic effects: The mean fetal heart rate increased to 20 bpm. The mean fetal arterial pressure increased to 10–15 mmHg. After desufflation pH, heart rate, and BP turned to normal. Hunter et al. also used nitrous oxide as insufflating gas. Under the same conditions, there were no effects on fetal blood gas values, heart rate, and BP. This indicates that fetal tachycardia and hypertension are caused by hypercarbia and not by increased IAP. The conclusion was that the pneumoperitoneum does not appear to create a significant risk to the healthy fetus and induces progressive, albeit reversible, fetal hypercarbia, acidosis, and tachycardia when pneumoperitoneum pressures exceeded 15 mmHg. These effects were minimized by using low pneumoperitoneum pressures or by using nitrous oxide as the insufflation gas [72]. The potential deleterious effects of short-term fetal hypercarbia are unknown. However, in high- risk mothers prone to hypercarbia (e.g., chronic lung disease, massive obesity), precautions to decrease maternal hypercarbia by using low-pressure pneumoperitoneum (12 mmHg or less) or nitrous oxide as the insufflation gas might be considered. Nitrous oxide has been safely employed during gynecologic laparoscopy.

Others also assumed that an IAP ≤15 mmHg has no risks. The intrauterine pressure during contractions of the uterus and coughing (represent only intermittent and short periods) is much higher [77–79].

Nitrous oxide requires the presence of either hydrogen gas or methane (such as from colonic origin) to be combustible during electrosurgical procedures [72].

The introduction of gas into the peritoneum (closed cavity) has two immediate effects: (1) increase in IAP and (2) gaseous exchange leading to equilibrium with gases in the blood [80]. Increased IAP can decrease cardiac output by several mechanisms, including direct alteration of venous resistance in the inferior vena cava, total peripheral resistance, and mean systemic pressure [80]. Impaired venous return via compression of the inferior vena cava is of particular concern in the second half of pregnancy since the enlarged uterus can also limit venous return. The uterine compression of vena cava can be minimized by lateral tilt (see Sect. 22.1.3). The CO_2 that is absorbed across the peritoneal surface first equilibrates within the bloodstream, then with longer operative time with the skeletal muscle, viscera, and finally bone. The patients who undergo a prolonged laparoscopic procedure are at risk of maintaining hypercarbia and acidosis postoperatively until all excess CO_2 is eliminated from the tissue. Hypercarbia and respiratory acidosis can be monitored to some extent by capnography which measures end-tidal CO_2 concentration in the endotracheal tubes. If a rise in end-tidal CO_2 is detected, CO_2 elimination via the alveoli can be increased using controlled hyperventilation. The limitation of capnography is that while it is sensitive, end-tidal CO_2 is not foolproof in estimating CO_2 arterial pressure. When a ventilation–perfusion mismatch is present and the amount of ventilation is greater relative to perfusion, gas from such ventilation will contain less pCO_2 than the actual $PaCO_2$, resulting in falsely normal or low end-tidal CO_2 readings [81]. A similar discrepancy between end-tidal CO_2 and $PaCO_2$ and subsequent acidosis has been demonstrated also in operative laparoscopy patients with compromised cardiopulmonary status [82]. For such patients, monitoring of arterial $PaCO_2$ and pH is preferable to limit the risk of hypercarbia and acidosis. The close monitoring of CO_2 is also important considering the potential direct effect of CO_2 in increasing the mean arterial pressure and total peripheral resistance index, leading to increased afterload which could limit cardiac output [83].

Limited studies of pneumoperitoneum in pregnant sheep have demonstrated increased fetal arterial BP tachycardia, and respiratory acidosis, which were only partially corrected with alteration in ventilator settings based on maternal capnography results [72, 84]. Intraperitoneal CO_2 pressures of ≤12 mmHg are recommended in order to prevent fetal acidosis [85]. CO_2 pneumoperitoneum created minimal impact on the patient and the fetus when IAP ≤15 mmHg is used [72, 86]. Some authors use a pneumoperitoneum of 10 mmHg—low enough to be in the safe range and high enough to gain adequate visualization for a safe procedure [87, 88].

Questions arise regarding the risk for decreased uterine blood flow due to increased IAP from insufflation and the possibility of fetal CO_2 absorption. CO_2 used for the creation of pneumoperito-

neum could lead to fetal CO_2 absorption with potential subsequent fetal acidosis. This could be minimized with the maintenance of IAP <12 mmHg and minimizing operative time. Clinical and experimental studies found no substantial adverse effects on the fetus when the maximal pneumoperitoneum pressure was limited to 10–12 mmHg and duration of less than 60 min [86, 89]. Sheep fetus has sufficient placental flow reserves or compensatory responses to maintain adequate gas exchange during a 1 h, 20 mmHg pneumoperitoneum [90]. Others stress the importance of the absorption of carbon monoxide, produced by the use of monopolar energy, through the peritoneum. The absorbed carbon monoxide can produce carboxyhemoglobin and methemoglobin that compete with hemoglobin in the uptake and transport of oxygen. It is recommended to continually remove the smoke produced by tissue fulguration, and increased levels of carboxyhemoglobin were not detected [91, 92]. Harmonic scissors produce vapor-free gas, avoiding the potential effects of carbon monoxide [93]. Another negative effect of electrocautery is the potential for uterine irritation. The CO_2 insufflation into the amniotic cavity of anesthetized ewes produced severe fetal hypercapnia, despite normal maternal CO_2 pressure and pH [94]. However, the possible negative effect of CO_2 pneumoamnion is most relevant to the future use of fetal surgery and should not be extrapolated to intraperitoneal surgery.

A decrease in cardiac output may place the placental and fetal blood flow at risk. However, it was demonstrated that the effect of increased IAP on the venous return is volume dependent [95]. In relatively hypovolemic subjects, increased IAP decreases venous return. This effect is a result of elevated venous resistance that is greater than the concomitant increase in mean systemic pressure. Conversely, in relatively hypervolemic subjects, increased IAP causes only minimal compression of the inferior vena cava, and increased mean systemic pressure "pumps" the blood into the inferior vena cava. This effect causes increased venous return and increased cardiac output resulting from the Starling mechanisms [95]. Therefore, because pregnancy is associated with a marked increase in circulating blood volume, pregnant women usually are hypervolemic, and the pneumoperitoneum should not lead to lower cardiac output or decreased fetal flow. Moreover, moderately increased IAP to the level usually used at laparoscopy (12–15 mmHg) was shown to increase preload at the beginning of pneumoperitoneum as a result of "milking" pooled blood from the splanchnic veins to the systemic circulation and forcing blood to the intravascular compartment from the compressed liver and spleen [96–98].

Maternal respiratory acidosis is easily corrected by the anesthesiologist, but the end-tidal CO_2 may not reflect true pCO_2 and acid–base balance in the fetus. Alterations in ventilator settings based on maternal end-tidal CO_2 resulted in late and incomplete correction of respiratory acidosis; it has therefore been suggested that one follow arterial blood gases for correct monitoring, especially because the end-tidal CO_2 significantly underestimates maternal pCO_2 by 15 mmHg and lags behind it [72]. Hunter et al. showed fetal hypercarbia, acidosis, possible tachycardia, and an increase in fetal arterial pressure with the use of a CO_2 pneumoperitoneum [72]. Again, negative long-term effects of these physiologic alterations on the fetus are not found but should be avoided if possible by close monitoring of maternal indices.

An N_2O pneumoperitoneum showed none of the "acidotic" changes of CO_2 pneumoperitoneum, but this gas has traditionally not been used because of combustion concerns [72]. Experience with gasless laparoscopy is limited with only 44 patients operated in pregnancy [99, 100].

22.2.2.3 Burst Abdomen

Definition

Burst abdomen represents the partial or complete separation of an abdominal wall wound with protrusion or evisceration of abdominal contents. It should be distinguished from wound dehiscence. *Wound dehiscence* and *incisional hernia* are part of the same wound failure process; it is the timing and the healing of the overlying skin that distinguishes the two. Dehiscence of the wound occurs before cutaneous healing, while incisional hernias (see Chap. 5) lie under a well-healed skin incision. Evisceration can occur after ischemia and subsequent dehiscence of the skin overlying hernia due to increased IAP. This condition is most commonly seen with (incarcerated) uterus in giant umbilical hernia (see Chap. 5).

Incidence

Available literature of burst abdomen during pregnancy revealed several cases due to incisional hernias [101, 102], umbilical hernias [103, 104], and surgical site infections post laparotomy [105, 106]. Intra-abdominal sepsis in pregnancy is rare and abdominal wall dehiscence following intra-abdominal sepsis is even rarer.

22.2.2.4 Acute Pancreatitis

See Chap. 3.

22.2.2.5 Intestinal Obstruction

See Chap. 11.

22.3 Clinical Presentation

The diagnosis of peripartum ACS is challenging not only due to the lack of well-established normative pregnant values of IAP but also because of the overlap of signs and symptoms between ACS and severe preeclampsia such as oliguria and nonspecific abdominal pain [8]. Abdominal distention is always present. Percussion reveals intraperitoneal fluid or tympanism (drumlike distention) characteristic for bowel obstruction or paralytic ileus. BP differentiates between preeclampsia/eclampsia (elevated) and septic or hemorrhagic shock. BP should be checked every several hours or when the clinical condition changes and deteriorates because patients with elevated BP with HELLP syndrome can develop hepatic rupture with hemoperitoneum resulting in fall in BP [9].

Burst abdomen, as a possible consequence of IAH/ACS in pregnancy, is easy to detect clinically. The condition may manifest following straining or removal of the skin sutures. Patients often note "ripping sensation" or a feeling that "something has given way." Impeding abdominal wall dehiscence is often preceded by the appearance of a salmon-pink serous discharge from the wound.

22.4 Diagnosis

Diagnostic workup should include the detection of IAP, IAH, and ACS itself and the underlying pathophysiologic process that leads to increased IAP. Both nonoperative (see Sect. 22.2.1) and operative conditions (see Sect. 22.2.2) should be searched for.

22.4.1 Intra-Abdominal Pressure Measurement

While the clinical examination is inaccurate for detecting raised IAP, IAH, and ACS, the diagnosis should rely upon accurate serial or continuous IAP measurements [107]. There is an increasing number of IAP measurement techniques.

> Trans-bladder measurement remains a commonly used method and was recommended by the WSACS in 2006 due to its simplicity and low cost [15, 108].

22.4.2 Laboratory Findings

Hematocrit, hemoglobin, platelets, bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase are needed for the diagnosis of HELLP syndrome [8]. Serum amylase and lipase levels three times over normal upper levels indicate acute pancreatitis (see Chap. 3). The underlying intraperitoneal infection, for example, after transvaginal oocyte retrieval, can develop in the form of an abscess and primary or secondary peritonitis [64]. Raised C-reactive protein level and leukocytosis indicate an underlying infection. New-onset proteinuria indicates preeclampsia/eclampsia. Blood urea nitrogen and creatinine levels reveal the severity of the acute renal failure.

22.4.3 Plain Chest X-Ray

Chest X-ray can reveal pulmonary edema or pleural effusion as a consequence of intra-abdominal pathology with IAH.

22.4.4 Abdominal Ultrasound

Transabdominal ultrasound can reveal a large quantity of free intraperitoneal fluid. It is useful for

detection of underlying pathologies, such as large polycystic ovaries in OHSS and acute pancreatitis (see Chap. 3). Transvaginal ultrasound is better for the definition of gynecologic causes of IAH.

22.5 Treatment

22.5.1 Nonoperative Treatment

22.5.1.1 Nutrition

Nutrition is a key component in the recovery of patients following severe injury or abdominal sepsis. The open abdomen is a significant source of protein and nitrogen loss (up to 2 g/day) in general population [109], and failure to account for this may lead to malnutrition with the overall poor outcome. This is even more pronounced in the pregnant patients due to additional nutritional requirements of the fetus. Protein deficiencies are also a risk factor for abdominal wall dehiscence.

Enteral feeding does not increase the risk of ACS [110], and it is safe within 36 h of damage control laparotomy [111–113] in general population. There are no larger studies on pregnant population. This concept has demonstrated increased rates of fascial closure and decreased infectious complications with early enteral nutrition.

22.5.1.2 Medical Treatment

Management of the underlying disease, such as OHSS, decreases the amount of intraperitoneal fluid and therefore IAP and IAH. Treatment ranges from conservative observation to intensive care admission with IAP monitoring and paracentesis to relieve ACS [44, 45]. Many consider polycystic ovaries as the most important risk factor for OHSS [64]. Insulin resistance, hypothyroidism, and hyperprolactinemia are the most common causes of polycystic ovaries. Only after the endocrine disorders are addressed (levothyroxine and metformin) OHSS and IAP can be successfully treated [64].

22.5.1.3 Paracentesis

Bedside abdominal decompression using paracentesis has been described in general population as a minimally invasive method to relieve elevated IAP after massive fluid resuscitation [114]. However, this modality is not indicated when hemorrhage is involved. Technical difficulties are present especially in advanced pregnancy when free intraperitoneal space is limited due to enlarged uterus.

22.5.2 Operative Treatment

Indications for laparo(s)tomy are [115, 116]:

- Oliguria
- Hypotension
- Acidosis
- Intraoperatively found risk factors for IAH/ACS
- Abdominal sepsis (selective, with/without IAP measurements)

22.5.2.1 Source Control

Removal of the underlying cause, for example, as in Meigs' syndrome [67], has two therapeutic implications: (1) removal of the (functional) pathologic process itself and (2) the decrease of IAP due to the removal of bulky tumor/mass.

22.5.2.2 Planned Relaparotomy

As a rule, following 24–48 h after the initial surgery for intra-abdominal sepsis or suspected organ vitality, the patient should be taken back to the operating room for reoperation. Reoperation should be performed in this time frame because (1) the abdominal exploration, lavage, drainage, and source control may be more difficult later due to the intraperitoneal adhesions and risks of enteric injury [117] and (2) the progress of organ ischemia, mostly bowel, does not result in ischemic perforation and (stercoral) peritonitis during this period.

22.5.2.3 Decompression Laparotomy

The ideal temporary abdominal closure (TAC) method should [118]:

- Protect the abdominal contents
- Prevent evisceration
- Allow removal of infected or toxic fluid from the peritoneal cavity
- Prevent the formation of fistulas
- Avoid damage to the fascia

- Preserve the abdominal wall domain
- Make reoperation easy
- Safe
- Facilitate definitive closure

Intraoperatively, diffuse bowel edema is noted; free intraperitoneal fluid or blood [9] should be evacuated. After several abdominal washouts with Ringer's lactate on 37–40 °C, the type of the laparotomy closure is chosen [8]. Many different techniques of TAC have been introduced, but patient groups remain small, with a high heterogeneity, making a comparison of techniques and outcomes difficult [119]. Various advantages and disadvantages of different forms of TAC are summarized in Table 22.1. There are no randomized controlled trials involving the use of negative-pressure wound therapy in gravid patients due to the rarity of such cases. Among many techniques developed for open abdomen management in general population, vacuum-assisted closure (VAC) allows currently the best results in terms of primary abdominal wall closure [120]. In some series of nonpregnant patients, using VAC protocols, complete fascial closure rate was achieved in 100% [121]. In abdomen with the constantly growing gravid uterus and low intra-abdominal pressure requirements, primary closure appears to be a particularly challenging. It is nevertheless a key endpoint in a pregnant woman, in order to protect the fetus and to assure a vaginal delivery.

Decompression laparotomy with TAC (Fig. 22.5) is indicated due to the presence of ACS not the cause of ACS [8]. Delayed repair by bridging biological meshes in the management of open abdomen has not been completely clarified and may result in bulging or recurrences in general population [122].

If the definitive fascial closure is not possible, another option may be skin-only closure to cover the exposed viscera and protect it, minimizing further injury to the exposed bowel. Ostomies should be placed as lateral as possible to be adequate [123].

Table 22.1 Advantages and disadvantages of different types of temporary abdominal closure techniques (Reproduced from [117] under the CC BY 4.0)

Technique	Equipment	Advantages	Disadvantages
Skin-only closure	Skin staples, towel clips, or sutures	Cheap, available, minimizes heat and fluid loss	Damage to the skin, risk of evisceration, no control of fluid loss, incidence of ACS
"Bogota" bag	Sterile 3 L saline bag cut and shaped and sutured to fascial edges	Cheap, available, minimizes heat and fluid loss	Damage to the fascial edges, the risk of evisceration, no control of fluid loss. Allows some assessment of intestinal viability
Opsite sandwich technique	Polyethylene sheet, Opsite dressings, abdominal packs, two suction drains, and wall suction	Cheap, available, minimizes heat and fluid loss is controlled and measurable	Incomplete fluid control and need for available wall suction
Absorbable mesh	Vicryl or similar mesh	Absorbable mesh, infection resistance, protects from evisceration, can be skin grafted	High rate of subsequent incisional herniation
Nonabsorbable mesh or commercial "zipper"	Commercial Wittmann patch	Abdominal reexploration is easy, maintains abdominal domain, gradual abdominal closure possible	Commercial equipment required and multiple trips to the operating theater usually required for closure
Vacuum-assisted closure (VAC)	Commercial equipment	Prevents loss of abdominal domain, collects and monitors fluid loss, decreases ACS, no damage to skin or abdominal fascia	Expensive commercial equipment required. Usually requires general anesthesia (GA) to change VAC system

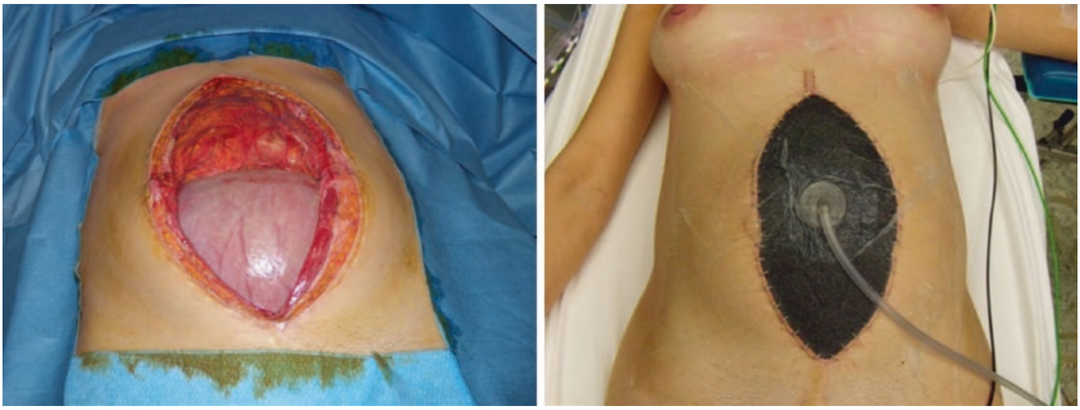


Fig. 22.5 Open abdomen. (**a**) The gravid uterus is seen in the inferior half of the laparostomy; (**b**) the open abdomen "closed" with vacuum-assisted closure (Reproduced from [124] under the CC BY 2.0)

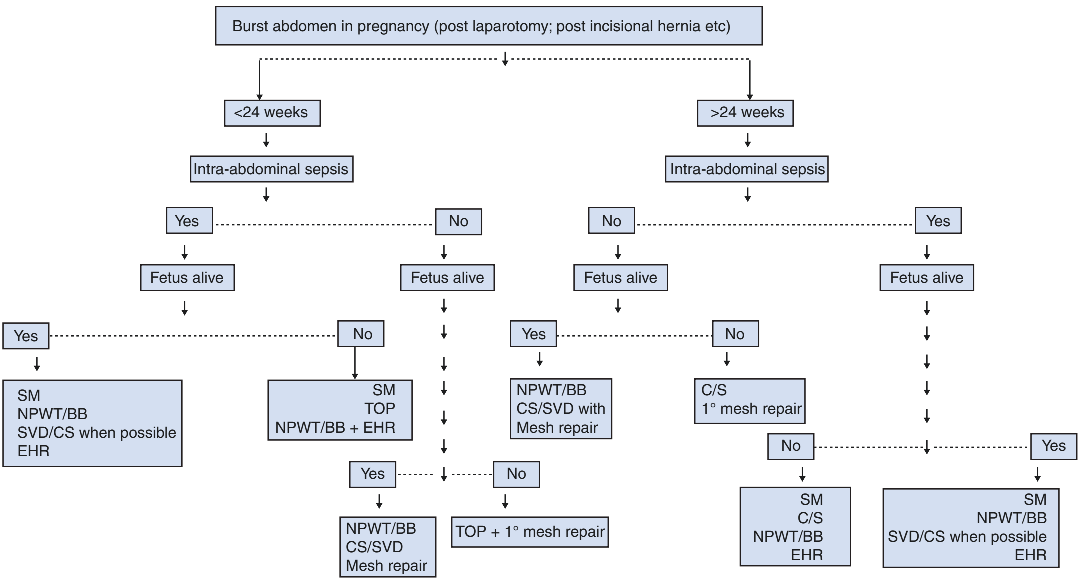


Fig. 22.6 Management algorithm for burst abdomen in pregnancy. *SVD* spontaneous vaginal delivery, *NPWT* negative-pressure wound therapy, *CS* Cesarean section, *TOP* termination of pregnancy, *SM* surgical management involves laparotomy and peritoneal lavage if required, *BB* Bogota bag, *EHR* elective hernia repair. Reproduced with permission from [106]

22.5.2.4 Burst Abdomen

The management of burst abdomen is a difficulty to both the surgeon and the obstetrician. Whether to close or not to close the abdomen and when and how to deliver the fetus depend on both maternal and fetal factors which must be considered for optimal outcome. Therapeutic principles in pregnancy are the same as in nonpregnant population with the possibility of one additional procedure for lowering IAP and salvage of the fetus – CS (Fig. 22.6).

22.5.3 Therapeutic Delivery

Similarities were identified in the pattern of progressive multi-organ dysfunction in both IAH and preeclampsia. A striking similarity is a definitive

treatment, for ACS, abdominal decompression, and for preeclampsia, delivery of the fetus and placenta, thereby affecting abdominal decompression. The placenta is the mediating factor for the maternal systemic inflammatory response, and it is thought that delivery of the placenta is the cure for preeclampsia. Therapeutic delivery as a modality of treatment of underlying cause is presented in various chapters depending on the cause.

Indications for CS are obstetric. Fetal distress is an indication for the emergent CS of the viable fetus. The fetus is considered viable at age 24 weeks. Fetal heart rate less than 100 bpm, prolonged deceleration for more than 1 min, or recurrent late decelerations should prompt emergent delivery [125]. The survival of infants born at 23–25 weeks of gestation was only 40% compared with those delivered at 26 weeks (80%) after maternal trauma. Maternal cardiopulmonary resuscitation is another scenario that requires emergent CS (see Chap. 10).

22.6 Prognosis

22.6.1 Maternal Outcome

22.6.1.1 Burst Abdomen

Various methods for (temporary) closure of burst abdomen in pregnancy were performed: two cases with negative-pressure wound therapy [105, 126], one with the mesh [102] and one with Bogota bag [106]. Maternal mortality was 0%.

22.6.2 Fetal Outcome

22.6.2.1 Burst Abdomen

Fetal mortality depends on (1) the gravid uterus incarceration at presentation and (2) gestation less than 24 weeks [102, 105, 106, 126].

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23 Acute Abdomen-Induced Preterm Labor

Abstract

The specific issue with acute abdomen during pregnancy is that many underlying conditions result in inflammation and infection which raise prostaglandin levels which are crucial for the normal progress of labor. Therefore, it is mandatory to stop the increased preterm production of prostaglandins. The only solution is early diagnosis and treatment of acute abdominal conditions during pregnancy. In addition to inflammation, abdominal trauma is also an issue. It can cause placental abruption and preterm labor. In addition to these two most common groups of the acute abdomen during pregnancy, other important topics are discussed. These include maternal and fetal stress as a result of any cause of acute abdomen during pregnancy and the problem of adequate perioperative nutrition. Inadequate maternal nutrition is present in some diseases with prolonged course before therapeutic interventions such as conservatively treated acute cholecystitis or acute pancreatitis. Prolonged inadequate postoperative nutrition is seen after many surgical procedures especially in those that require bowel resections or reoperations. Therefore, the underlying pathology should be diagnosed and treated early in the course of the disease, and additional measures for detection and prevention of preterm labor should be instituted as early as possible.

23.1 Definitions

Preterm labor (PTL) is usually defined as regular contractions accompanied by the cervical change between 20 0/7 and 36 6/7 weeks of gestation. The obstetric causes leading to PTL are:

- Delivery for maternal or fetal indications, in which labor is either induced or the infant is delivered by elective or emergent Cesarean section (CS)
- Spontaneous PTL with intact membranes
- Preterm premature rupture of the membrane (PPROM), irrespective of the type of delivery

PPROM is defined as spontaneous rupture of the membranes at less than 37 weeks of gestation at least 1 h before the onset of contractions. About 30–35% of PTLs are indicated, 40–45% follow spontaneous PTL, and 25–30% follow PPROM; births that follow spontaneous labor and PPROM are together designated as spontaneous PTLs [1].

23.2 Physiology of Labor

Inflammation is central to reproductive success. Ovulation, menstruation, implantation, and parturition are all inflammatory processes. It has been proposed that the fundamental difference between term labor and PTL is that the former

G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4_23

results from "physiologic activation" of this common pathway, whereas PTL results from either early idiopathic activation of the normal labor or disease process ("pathologic activation") that activates one or more of the components of the common pathway [2].

The *common pathway of parturition* is defined as the anatomic, biochemical, immunologic, endocrinologic, and clinical events that occur in the mother and fetus in both term and PTL. Fetal cortisol is central to labor initiation in sheep [3]. Ablation of the fetal hypophysis or adrenal glands, or both, prevents the initiation of parturition. The same mechanism might be implicated in parturition in women [4]. Theories proposed to explain the initiation of term labor are (1) progesterone withdrawal, (2) oxytocin initiation (not proven), and (3) decidual activation. As parturition nears, the fetal adrenal axis becomes more sensitive to the adrenocorticotropic hormone, increasing the secretion of cortisol. Fetal cortisol stimulates placental 17α-hydroxylase activity, which decreases progesterone secretion and increases estrogen production. The reversal in the estrogen/progesterone ratio results in increased prostaglandin formation, initiating a cascade of events resulting in labor (see Sect. 23.2.4). In human, serum progesterone concentrations do not fall as labor; therefore, a decrease in local progesterone concentrations or in the number of receptors is a plausible mechanism for initiation of labor [4–6]. During pregnancy, the uterus is maintained in a relatively quiescent state through the separate or combined autocrine–paracrine actions of inhibitors such as progesterone, prostacyclin (PGI2), relaxin, parathyroid hormone-related peptide, calcitonin gene-related peptide, adrenomedullin, vasoactive intestinal peptide, nitric oxide, and corticotropin-releasing hormone, which may both inhibit and stimulate uterine contractility [7].

Activation of the uterine components of the common pathway of parturition may be synchronous or asynchronous. *Synchronous activation* results in clinical spontaneous PTL. *Asynchronous activation* results in a different phenotype. For example, predominant activation of the membranes leads to PPROM, that of the cervix to cervical insufficiency, and that of the myometrium to preterm uterine contractions without cervical change or rupture of membranes.

23.2.1 Myometrial Contractility

Increased cell-to-cell communication is thought to be responsible for the effectiveness of myometrial contractility during labor. Gap junctions develop in the myometrium just prior to labor and disappear shortly after delivery [8, 9]. Gap junction formation and the expression of the gap junction protein, connexin-43, in human myometrium are similar in both term labor and PTL [10–12]. The appearance of gap junctions and increased expression of connexin-43 may be part of the underlying series of molecular and cellular events responsible for the switch from contractures to contractions before the onset of parturition. Estrogen, progesterone, and prostaglandins have been implicated in the regulation of gap junction formation, and they also influence the expression of connexin-43 [13–15]. Connexin-43 and other distinct proteins are called contraction-associated proteins that are characteristic of this phase of parturition [16–18]. α-Actin was expressed in the myometrium in early pregnancy, whereas γ-actin was highly expressed by myometrium with a contractile phenotype.

The concept of myometrial phenotype programming [19] proposed and provided evidence that the myometrium undergoes sequential phenotypic change starting from an early proliferative phase (characterized by bromodeoxyuridine incorporation, the proliferating cell nuclear antigen expression level, increased IGF-I signaling, and expression of anti-apoptosis factors such as Bcl-2) [19], an intermediate synthetic phase (characterized by increased cell size and synthesis/deposition of interstitial matrix that forms the ground substance of the myometrium) [20–22], and a late contractile phase (upregulation of contraction-associated proteins, oxytocin, and prostaglandin receptors) in which the cells are committed to labor [12, 23, 24]. This phenotypic programming is accomplished through two separate but integrated pathways: an endocrine

cascade comprising the fetal hypothalamic–pituitary–adrenal–placental axis and a mechanical pathway in which fetal growth imposes tension on the uterine wall [7].

23.2.2 Cervical Remodeling

The changes in the cervix include (1) softening, (2) ripening, (3) dilatation, and, after delivery, (4) repair [25]. The molecular and cellular bases for cervical remodeling during pregnancy and parturition are largely dependent on the regulation of extracellular matrix components [25, 26]. Softening of the cervix begins in early pregnancy. The tensile strength of the softened cervix appears to be maintained by an increase in collagen synthesis and growth of the cervix. Cervical ripening is characterized by a decreased concentration of collagen and the dispersion of collagen fibrils. The latter has been attributed to glycosaminoglycans, such as decorin and hyaluronan, which promote hydration of cervical tissue and dispersion of the collagen fibers [26]. Dilation of the cervix is an inflammatory phenomenon in which there is an influx of macrophages and neutrophils and matrix degradation [27, 28]. Chemokines such as IL-8 [29, 30] and S100 proteins [31, 32] attract inflammatory cells, which, in turn, release proinflammatory cytokines, including IL-1β [33, 34] and tumor necrosis factor-α (TNF-α) [32], that can activate the nuclear factor (NF)-κB signaling pathway. NF-κB can block progesterone receptor-mediated actions [35]. Progesterone has been implicated in the regulation of cervical remodeling because administration of antiprogestins to women in the midtrimester and at term induces cervical ripening [25, 36, 37].

23.2.3 Decidual/Membrane Activation

During pregnancy, the chorioamnionic membranes fuse with the decidua. In preparation for delivery, biochemical events lead to separation and postpartum expulsion of the membranes. Fibronectins are a family of important extracellular matrix proteins. The available evidence suggests that degradation of a heavily glycosylated form of cellular fibronectin – fetal fibronectin – which is present at the chorionic–decidual interface leads to its release into cervical and vaginal secretions immediately before term and PTL [38–40].

Enzymatic activity of matrix metalloproteinases (MMPs) and other proteases has been implicated in the process of rupture of membranes and parturition with intact membranes (with and without infection) [41, 42]. The precise mechanism of decidual/membrane activation remains unknown, but roles for extracellular matrix-degrading enzymes such as the MMPs and elastase have been proposed. There is an increased availability of MMP-1 (interstitial collagenase) [43], MMP-8 (neutrophil collagenase) [43], MMP-9 (gelatinase B) [44], and neutrophil elastase [45] in the amniotic fluid of women with PPROM, compared with women in PTL with intact membranes. Plasmin has also been implicated [40] because it can degrade type III collagen, fibronectin, and laminin [46]. A role for tissue inhibitors of MMPs (TIMPs) has also been postulated.

23.2.4 Prostaglandins and Parturition

Prostaglandins have been considered the key mediators for the onset of labor [47] because they can induce myometrial contractility [47, 48], changes in extracellular matrix metabolism associated with cervical ripening [49, 50], and decidual/membrane activation. Both COX-1 and COX-2 are present within the pregnant uterus. The expression of COX-1 remains constant throughout gestation, but there is an exponential rise in COX-2 activity throughout gestation in the fetal membranes, chorion-decidua, and myometrium with most of the increase occurring before the onset of labor. The fetal membranes are a major source of prostaglandin synthesis. Prostaglandin synthesis in fetal membrane explants is suppressed by COX-2-specific

inhibitors but not by COX-1-specific inhibitors. This demonstrates the importance of COX-2 in the production of intrauterine prostaglandins in the human. Labor is associated with increased COX-2 expression of messenger RNA (mRNA) and increased activity of this enzyme in amnion (a rate-limiting step in the production of prostaglandins). This increase in amniotic COX-2 activity is accompanied by decreased expression of the prostaglandin-metabolizing enzyme, 15-hydroxyprostaglandin dehydrogenase (PGDH), in the chorion. This would allow prostaglandins produced in the amnion to traverse the chorion and reach the myometrium, where they can stimulate smooth muscle contractions [51]. The biochemical mechanisms by which prostaglandins activate the common pathway of parturition are the following: (1) prostaglandins directly promote uterine contractions by increasing sarcoplasmic and transmembrane calcium fluxes and through increased transcription of oxytocin receptors, connexin-43 (gap junctions), and the prostaglandin receptors EP1 through EP4 and FP27 [52, 53]; (2) prostaglandins induce synthesis of MMPs by fetal membranes and cells within the uterine cervix (as noted, MMPs have been implicated in the mechanisms of membrane rupture and also in cervical ripening) [54, 55]; and (3) prostaglandin E2 (PGE_2) and $PGF_{2\alpha}$ increase the ratio of expression of the progesterone receptor (PR) isoforms, PR-A/PR-B [56]. This may induce a functional progesterone withdrawal.

23.3 Etiopathogenesis

Spontaneous PTL can be the result of (1) maternal conditions, (2) fetal conditions, and (3) placental conditions. This chapter will concentrate on the influence of localized/diffuse peritonitis and abdominal trauma on PTL. There are many factors that increase the rate of PTL, and localized or diffuse peritonitis in these settings probably synergistically increase the rate of PTL. The cause of membrane rupture is mostly unknown, but asymptomatic intrauterine infection is a frequent precursor. Risk factors for PPROM are generally similar to those for spontaneous PTL with intact membranes, although infections and tobacco exposure play important parts [57].

All spontaneous PTLs utilize a common biochemical pathway (see Sect. 23.3.4), which is employed by each pathogenic pathway which has distinctive genetic and/or epidemiologic risk factors and unique biochemical triggers. Mechanical stretching of the uterus resulting from multifetal gestations and cervical insufficiency is outside of the scope of this book.

23.3.1 Inflammation

Amniotic cavity is sterile for bacteria in 99% of cases. Infection is a frequent and important mechanism in PTL and the only pathologic process for which an unequivocal causal link with PTL has been established. Microorganisms can gain access to the amniotic cavity by (Fig. 23.1):

- Ascending from the vagina and the cervix
- Hematogenous dissemination through the placenta
- Accidental introduction at the time of invasive procedures
- Retrograde spread through the Fallopian tubes

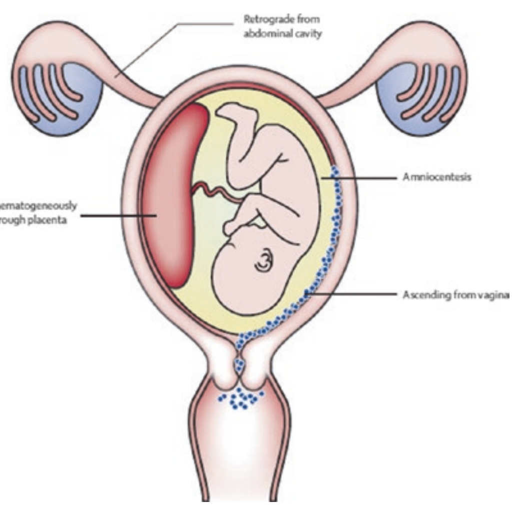

Fig. 23.1 Potential routes of intrauterine infection. Reproduced with permission from [58]

Evidence for causality includes:

- Intrauterine infection or systemic presence of microbial products (bacterial endotoxin).
- Extrauterine maternal infections (malaria, pyelonephritis, pneumonia, and periodontal disease) [59].
- Subclinical intrauterine infections (histological chorioamnionitis) [60].
- Intra-amniotic infection or inflammation (defined as an elevation of amniotic fluid concentrations of proinflammatory cytokines and matrix-degrading enzymes in the midtrimester) [61].
- Antibiotic treatment of ascending intrauterine infections can prevent PTL in experimental models of chorioamnionitis.
- Treatment of asymptomatic bacteriuria prevents PTL.

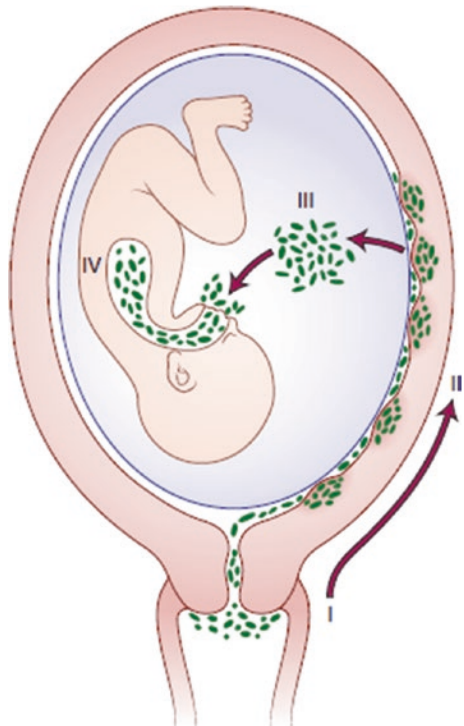

Fig. 23.2 The pathway of ascending intrauterine infection. Stage I refers to a change in microbial flora in the vagina and/or cervix. In stage II, microorganisms are located between the amnion and chorion. Stage III represents intra-amniotic infection, and stage IV is fetal invasion [66]

Evidence suggests that the extent of bacterial colonization, the route of infection, and the stimulatory capacity of the bacteria all play key roles in the activation of maternal and fetal proinflammatory signaling cascades. Almost all studies are based on genital tract infections causing intrauterine infection, and there are no large studies on the pathophysiology and microbiology of peritonitis and PTL.

Intrauterine inflammation is associated with approximately 25–40% of all PTLs [58, 62]. This is a conservative estimate due to the difficulty associated with detecting chorioamnionitis using conventional culture techniques [58]. Also, microbial footprints in the amniotic cavity detected by molecular microbiological techniques showed that women with a positive amniotic fluid *Ureaplasma urealyticum* PCR, but a negative culture, have similar rates of PTL as women with positive cultures for the same microorganism [63]. Furthermore, since the rate of microbial colonization of the chorioamnion is twice that seen in the amniotic cavity, rates of intrauterine infection based only on amniotic fluid cultures substantially underestimate the level of association [64].

Ascending intrauterine infection is considered to have four stages (Fig. 23.2). Stage I consists of a change in the vaginal and cervical microbial flora or the presence of pathological organisms (i.e., *Neisseria gonorrhoeae*) in the cervix. Some forms of bacterial vaginosis may be an early manifestation of stage I. Once microorganisms gain access to the intrauterine cavity, they reside in the decidua (stage II). A localized inflammatory reaction leads to deciduitis. Microorganisms may then reside in the chorion and amnion. The infection may invade the fetal vessels (choriovasculitis) or proceed through the amnion (amnionitis) into the amniotic cavity, leading to the microbial invasion of the amniotic cavity or an intra-amniotic infection (stage III). Rupture of the membranes is not a prerequisite for intra-amniotic infection because microorganisms can cross intact membranes [65]. Once in the amniotic cavity, the bacteria may gain access to the fetus by different ports of entry (stage IV).

Aspiration of the infected fluid by the fetus may lead to congenital pneumonia. Otitis, conjunctivitis, and omphalitis may occur by the direct spreading of microorganisms from the infected amniotic fluid. Seeding from any of these sites to the fetal circulation may result in fetal bacteremia and sepsis.

Microbial invasion of the amniotic cavity (MIAC) is present in 12.8% of women with PTL with intact membranes [67] and in 21–32% of those with PPROM [67, 68]. The majority of these cases (83%) are complicated by microbial-associated IAI. Sterile IAI is responsible for a small proportion of the pregnancies complicated by IAI (17–33%). The majority of women with PPROM have sterile inflammation [68, 69]. In these studies, different gestational week ranges and different IL-6 cutoff values for definition of intra-amniotic infection were used. Microbial invasion of the amniotic cavity was detected in 51% of patients with acute cervical insufficiency. Patients with MIAC are more likely to have PTL, have spontaneous ROM, and develop clinical chorioamnionitis than those with sterile amniotic fluid. The most common organisms found in the amniotic fluid are genital mycoplasmas. It is believed that ascending infection is the most common source of microbial invasion of the amniotic cavity, although transplacental infections may also occur. The lower the gestational age at which a patient presents with PTL and PPROM, the higher the frequency of MIAC. Moreover, many of these infections appear to be chronic in nature, because they have been detected in women having midtrimester amniocentesis for genetic indications. Bacterial products such as endotoxin have also been detected in the amniotic cavity of women with PTL and PPROM. Endotoxin has powerful proinflammatory effects in maternal and fetal tissues. Spontaneous ROM at term results from progressive weakening of the membranes because of collagen remodeling and cellular apoptosis and from increased intrauterine pressure with uterine contractions when membrane rupture occurs subsequent to the onset of labor. While PPROM near term likely results in most cases from these same physiologic processes, PPROM remote from term has been associated with several pathologic processes, especially infection and inflammation, membrane stretch, and local tissue hypoxia.

The pathogenesis of PPROM in ascending infection is due to bacterial proteases (collagenases and phospholipases) that can cause membrane weakening. Ascending bacterial colonization can also cause a local inflammatory response including the production of cytokines, prostaglandins, and metalloproteases which cause membrane degradation and weakening.

Microorganisms are “sensed” by the innate components of the immune system, which include (1) the soluble pattern recognition receptors (PRRs), lectin, and C-reactive protein; (2) transmembrane PRRs, which include scavenger receptors, C-type lectins, and Toll-like receptors (TLRs); and (3) intracellular PRRs, including Nod1 and Nod2, retinoic-induced gene type 1, and melanoma differentiation-associated protein 5, which mediates recognition of intracellular pathogens (e.g., viruses). The best-studied PRRs are the TLRs. Ligation of TLR results in activation of NF-κB, which, in turn, leads to the production of cytokines, chemokines, and antimicrobial peptides. Because TLRs are crucial for the recognition of microorganisms, it could be anticipated that defective signaling through this pathway would impair bacteria-induced PTL. Consistent with this thesis, a strain of mice bearing a spontaneous mutation for TLR-4 was less likely to deliver preterm after intrauterine inoculation of heat-killed bacteria or administration of lipopolysaccharide than wild-type mice. In pregnant women, TLR-2 and TLR-4 are expressed in the amniotic epithelium as well as in decidua. Moreover, spontaneous labor that occurs at term or preterm and is complicated by histologic evidence of chorioamnionitis, regardless of the membrane status (intact or ruptured), is associated with increased mRNA expression of TLR-2 and TLR-4 in the chorioamniotic membranes. These observations suggest that the innate immune system plays a role in parturition.

23.3.1.1 Proinflammatory Cytokines

Inflammation and its mediators, chemokines such as IL-8, the proinflammatory cytokines (IL-1α, TNF-α), and other mediators (e.g., platelet-activating factor, prostaglandins), are central to PTL induced by infection. IL-1 is an important cytokine implicated in the onset of PTL associated with infection: (1) IL-1 is produced by human decidua in response to bacterial products; (2) IL-1α and IL-1β stimulate prostaglandin production by human amnion and decidua; (3) IL-1α and IL-1β concentrations and IL-1-like bioactivity are increased in the amniotic fluid of women with PTL and infection; (4) intravenous IL-1α stimulates uterine contractions; and (5) administration of IL-1 to pregnant animals induces PTL, and this effect can be blocked by the administration of its natural antagonist, the IL-1 receptor antagonist (IL-1ra).

Evidence supporting the role of TNF-α in the mechanisms of PTL is similar: (1) TNF-α stimulates prostaglandin production by amnion, decidua, and myometrium; (2) human decidua can produce TNF-α in response to bacterial products; (3) amniotic fluid TNF-α bioactivity and immunoreactive concentrations are elevated in women with PTL and intra-amniotic infection; (4) in women with PPROM and intra-amniotic infection, TNF-α concentrations are higher in the presence of labor; (5) TNF-α can stimulate the production of MMPs, which have been implicated in membrane rupture; (6) TNF-α application to the cervix induces changes that resemble cervical ripening; (7) TNF-α can induce PTL when administered systemically to pregnant animals; and (8) TNF-α and IL-1α enhance IL-8 expression by decidual cells, and this chemokine is strongly expressed by term decidual cells in the presence of chorioamnionitis. There are many other cytokines and chemokines (IL-6, IL-16, IL-18, colony-stimulating factors, macrophage migration inhibitory factor, monocyte chemotactic protein-1, epithelial cell-derived neutrophil-activating peptide, etc.) implicated in the complex host response to pathogenic insults and infection-induced PTL. The redundancy of the cytokine network implicated in parturition is such that blockade of a single cytokine is insufficient to prevent infection-induced PTL. However, blockade of both IL-1 and TNF-α signaling pathways in mice was associated with a decreased rate of PTL, partly because IL-1 and TNF mediate their effects at least in part via COX-2 [70]. It is notable in this respect that even the combined inhibition of IL-1 and TNF-α does not result in complete abolishment of susceptibility to bacterially induced labor, suggesting that there are yet other important factors.

23.3.1.2 Anti-Inflammatory Cytokines

IL-10 is thought to be a key cytokine for the maintenance of pregnancy. Its concentrations are increased in intra-amniotic inflammation, suggesting that IL-10 may play a role in dampening the inflammatory response and may have therapeutic value. In a nonhuman primate model of intrauterine infection with pregnant rhesus monkeys, dexamethasone and IL-10 treatment significantly reduced IL-1α-induced uterine contractility. The amniotic fluid concentrations of TNF-α and leukocyte counts were also decreased by IL-10 treatment. Furthermore, the administration of IL-10 in animal models of infection has been associated with improved pregnancy outcome.

23.3.1.3 Cytokeratins

Early choriodecidual infection results in decreased cellular membrane integrity and tensile strength via dysfunction of cytokeratin networks. Downregulation of cytokeratin expression and perturbations in the amniotic epithelial cell intermediate filament network occur after group B streptococcus choriodecidual infection, which may contribute to PPROM (Fig. 23.3).

23.3.2 Maternal and Fetal Stress

The maternal stress of exogenous or endogenous origin is modestly associated with an increased risk for PTL. The stressful insult could occur in the preconceptional period or during pregnancy. The precise mechanism is unknown; however, a role for CRH has been proposed. This hormone was originally identified in the hypothalamus but is expressed by the placenta. The maternal plasma

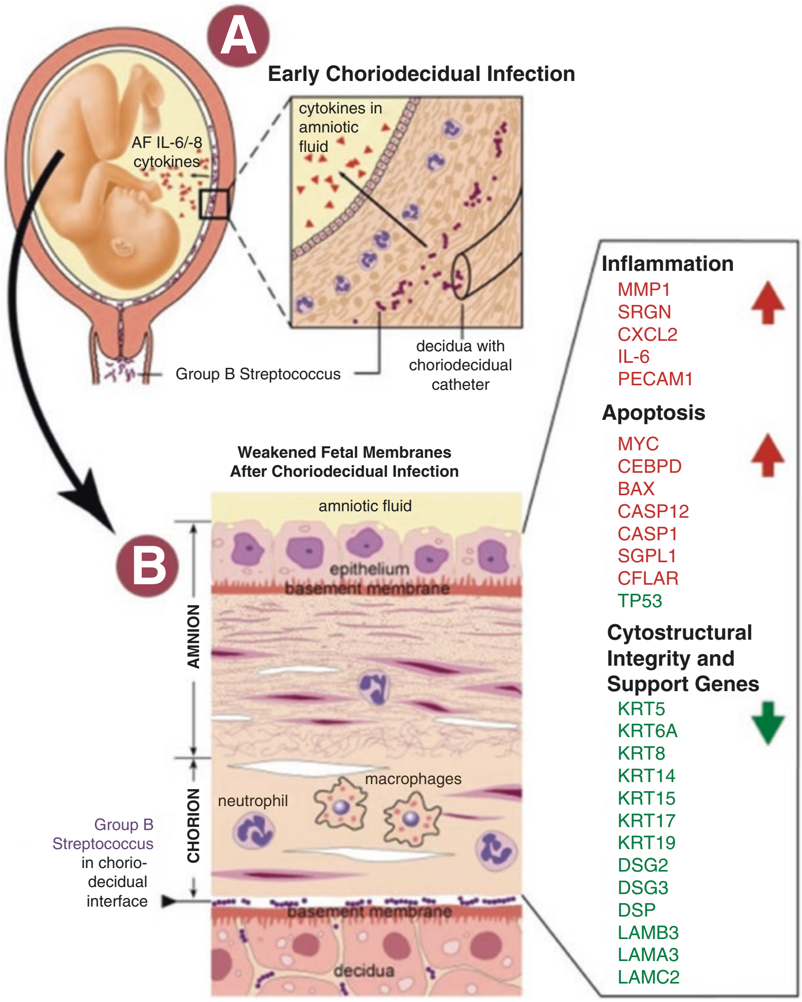

Fig. 23.3 The pathway of ascending intrauterine infection (Reproduced from [71] under the CC BY 4.0)

CRH concentrations increase during the second half of pregnancy and peak during labor, whereas serum concentrations of the CRH-binding protein decline during the third trimester. The trajectory of CRH serum concentration changes identifies women destined for preterm, term, and post-term delivery. The mechanisms regulating the serum concentration and trajectory of CRH have been described as "a placental clock." Because CRH maternal plasma concentrations are elevated in both term and PTL, it would appear that CRH is part of the common pathway of labor. The mechanisms through which CRH activates the common pathway of parturition include the following: (1) increased production of PGE_2 by amnion, chorion, and placental cells, but not by decidual cells; (2) increased production of $PGF_{2\alpha}$ by amnion, decidua, and placental cells, but not by chorion; (3) increased expression of MMP-9 by chorion and amnion; (4) stimulation of the release of adrenocorticotropic hormone (ACTH) from the pituitary gland to drive fetal cortisol production (this establishes a feed-forward cycle, because cortisol stimulates production of CRH by the placenta and fetal membranes); (5) induction of the synthesis of fetal DHEAS by the fetal adrenal zone (DHEAS serves as a source of estrogens, which in turn enhance the expression of the oxytocin receptor, COX-2, prostaglandin receptors, and connexin-43); (6) cortisol produced

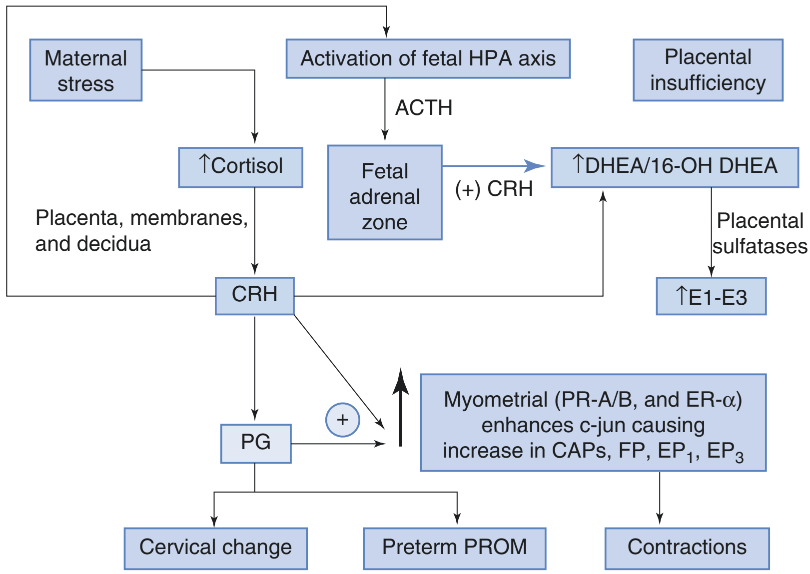

Fig. 23.4 Proposed pathways by which stress can induce preterm labor. *ACTH* adrenocorticotropic hormone, *CAPs* contraction-associated proteins, *CRH* corticotropin-releasing hormone, *DHEA* dehydroepiandrosterone, *E1–E3* estrone, estradiol, and estriol, *EP1* and *EP3* prostaglandin E receptors types I and III, *ER-α* estrogen receptor-α, *FP* prostaglandin F receptor, *HPA* hypothalamic–pituitary–adrenal, *PG* prostaglandin, *PR* prostaglandin receptor, PROM premature rupture of membranes. Reproduced with permission from [72]

in response to CRH can increase amnion COX-2 expression while inhibiting chorionic PGDH expression (resulting in a net bioavailability of prostaglandins); and (7) CRH inhibits progesterone production by the placenta. Figure 23.4 illustrates the molecular mechanisms for stress-associated PTL. As noted, CRH has been implicated in the mechanisms of spontaneous parturition at term. Therefore, this specific pathway may operate in normal-term labor as well as in PTL. In the former case, placental CRH expression reflects the maturation of the fetal hypothalamic–pituitary–adrenal axis; in the latter, it reflects physiologically stressful events occurring at later gestational ages. It may be surmised that some cases of PTL occurring close to term resort to the physiologic mechanisms used in term labor after fetal maturation has been accelerated by stressful stimuli.

Although the evidence discussed provides biologic plausibility for the concept that psychosocial stress may contribute to PTL risk via its effects on several stress-sensitive biologic processes implicated in parturition, tests of pathway (meditational) models to show these linkages have generally been unsuccessful. No known instance exists in biology at which a simple, one-to-one correspondence is present between a specific psychological and a specific biologic state. Cortisol production in vivo is influenced not only by the psychological state of the individual but also concurrently by a host of other conditions, such as variations in the nutritional milieu, physical activity, infection/inflammation, hypoxia, sleep, and chronobiological state, and, in the case of pregnancy, by the stage of gestation. Moreover, the effects of psychological stress on cortisol production likely vary as a consequence of these other conditions (i.e., an interactional, conditional, or effect modification model). Second, no instance in biology is known when perturbation within a particular biologic system remains constrained within that system. Adoption and implementation of a systems biology approach will be required to uncover the complex web of interrelationships and pathways inherent in vivo human models of complex multifactorial disorders such as PTL (Fig. 23.5).

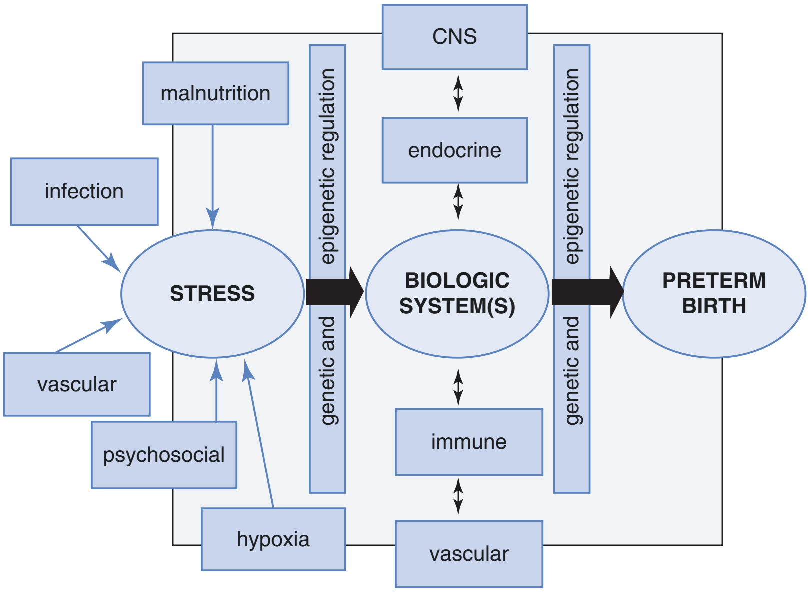

Fig. 23.5 Contribution of maternal stress and stress biology to preterm birth. No one-to-one correspondence exists between psychosocial stress and a stress-sensitive biology; the nature, magnitude, and duration of the effects of maternal psychosocial stress during pregnancy on any given stress-sensitive biologic system are likely altered by the context of other conditions/stressors, such as those related to nutrition, infection, and hypoxia. Similarly, the nature, magnitude, and duration of the effects of a given stress-sensitive biologic system in pregnancy on maternal and fetal target systems involved in parturition are likely altered by the secondary perturbations in other closely related biologic systems and their feedback effects. Reproduced with permission from [73]

23.3.3 Placental Abruption

Decidual hemorrhage (placental abruption) originates in damaged spiral arteries or arterioles and presents clinically as vaginal bleeding or either a retroplacental or retrochorionic hematoma formation noted on ultrasound. The association of abruption with increasing maternal age may reflect an increase in myometrial artery sclerosis which increases from 11 of spiral arteries at age 17–19 years to 83% after age 39 [74].

There are three principal mechanisms for initiation of placental abruption:

- Decidual spiral artery disruption
- Infection-induced placental abruption
- Trauma-induced placental abruption

23.3.3.1 Decidual Spiral Artery Disruption

The decidua is a rich source of tissue factor, the primary initiator of clotting through thrombin generation [75]. Following spiral arterial vascular disruption, decidual tissue factor is exposed to and can complex with plasma factor VII to generate factor Xa that, in turn, converts prothrombin to thrombin. Thrombin subserves a number of hemostatic functions to produce a retroplacental or retromembranous thrombus. However, in addition to its procoagulant properties, thrombin also enhances expression of tissue-type and urokinase-type plasminogen activator (uPA and tPA), which can directly degrade fibronectin, and generates plasmin from plasminogen which can degrade laminin, collagen III, and fibronectin, crucial components of the decidua and fetal membranes [76].

The expression of MMP-1 and MMP-3 protein is significantly enhanced by thrombin binding to its receptor, protease-activated receptor type 1 (PAR-1) [77, 78]. Thrombin also enhances MMP-9 expression [79]. Abruption-associated PPROM is accompanied by dense decidual neutrophil infiltration in the absence of infection [80]. Neutrophils are a rich source of elastase and MMP-9 [81] which contribute to PPROM and cervical effacement. These findings suggest that a

mechanism linking abruption-associated PPROM to decidual thrombin–PAR interactions triggers myometrial contractions [82].

23.3.3.2 Infection-Induced Placental Abruption

With maternal intraperitoneal infection, microorganisms may gain access to the intervillous space by hematogenous dissemination during maternal bacteremia. From there, the infection could spread to the villi and fetal circulation. Confirmation of this theory is that histological chorioamnionitis and funisitis are present significantly more often in patients with acute, severe preterm placental abruption than in normal deliveries [83]. Another route could be the retrograde transport of bacteria through the Fallopian tubes causing chorioamnionitis. Direct bacterial colonization of the decidua in generalized peritonitis with resultant tissue inflammation may initiate processes, such as disruption of decidual lysosomes, in addition to tissue disruption, that ultimately result in placental abruption [84].

23.3.3.3 Trauma-Induced Placental Abruption

In an uncompromised pregnancy, a large retroplacental hematoma involving the central area and up to 40% of the maternal surface will cause fetal embarrassment, while smaller retroplacental hematomas may prove equally embarrassing in pregnancies where the maternal blood supply is diminished, as in maternal hemorrhagic shock. An association has been noted between premature delivery, PROM, and peripheral placental hemorrhage [85].

Retroplacental hemorrhage should be distinguished from placental abruption, which is a clinical diagnosis, where there is a premature separation of the placenta from the maternal surface with decidual hemorrhage.

The overall incidence of placental abruption is about 0.5%, and a history of placental abruption increases the risk of a similar episode in a subsequent pregnancy by tenfold [86]. The true incidence of PTL following trauma during pregnancy is unknown. It appears to be under 5% [87, 88].

There are two pathophysiologic mechanisms for traumatic placental abruption. First is mechanical (see Sect. 10.3.5.1). Another, on a cellular level, is when a traumatic injury to the uterus results in destabilization of lysosomal enzymes that can initiate prostaglandin production. Additional predisposing factors, such as cigarette smoking and cocaine use, can increase the incidence, presumably as a result of decidual necrosis. The incidence of placental abruption is also increased in preeclampsia, diabetes mellitus, multiple births, short umbilical cord, and velamentous cord insertion [89, 90]. However, in many cases, no cause of placental abruption can be identified. In general, infants born after placental abruption are significantly smaller for gestation than controls. Most studies report a perinatal death rate following abruption in general pregnant population at approximately 50% is related to the strong association with PTL and, paradoxically, is higher for singleton than multiple births [90].

23.3.4 Maternal Nutritional Status

Many causes of fetal morbidity in addition to PTL are due to the loss of adequate maternal nutrition during pregnancy. In general pregnant population, a low prepregnancy BMI is associated with a high risk of spontaneous preterm birth, whereas obesity can be protective [91]. Women with low serum concentrations of iron, folate, or zinc have more preterm births than those with measurements within the normal range [92, 93]. Maternal thinness is associated with decreased blood volume and reduced uterine blood flow which can increase the rate of PTL [94].

When the acute abdomen is present during pregnancy, there are three scenarios for protracted maternal starvation:

- Recurrent or persistent symptomatology of underlying disease such as symptomatic cholelithiasis/cholecystitis, acute/chronic pancreatitis, adnexal torsion, etc.
- Postoperative catabolism with inadequate intravenous supplementation
- Protracted posttreatment sepsis/septic shock

In all these scenarios, peroral nutrition is mostly inadequate in addition to higher basal

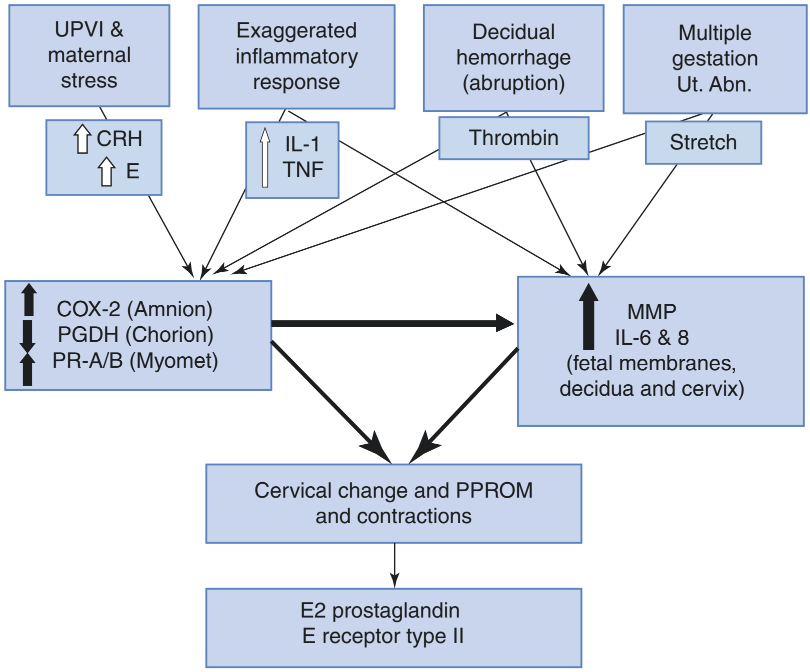

Fig. 23.6 Pathogenesis of preterm delivery (PTD). *COX-2* cyclooxygenase 2, *E2* prostaglandin E receptor type II, *IL* interleukin, *MMP* metalloproteinase, *PGDH* 15-hydroxyprostaglandin dehydrogenase, *PR-A/B* *PPROM* preterm premature rupture of the membranes, *TNF* tumor necrosis factor, *UPVI* uteroplacental vascular insufficiency, *Ut Abn* uterine abnormality. Reproduced with permission from [99], *PR-A/B* prostaglandin receptor

metabolism in systemic inflammation leading to body mass loss. Due to blood redistribution in sepsis, uterine blood flow can further be decreased.

23.3.5 Final Common Pathway

The generation of prostaglandins and proteases reflects the final common pathway of delivery, whether occurring preterm or at term. Prostaglandin levels increase in reproductive tract tissues, maternal plasma, and amniotic fluid immediately prior to and during parturition [95, 96]. Concomitant with rising prostaglandin levels is the upregulation of myometrial prostaglandin receptors prior to the onset of labor [97, 98]. Prostaglandins induce functional progesterone withdrawal, enhance sensitivity to estrogens, and increase MMP and IL-8 expression. Moreover, all the pathways of prematurity described above also directly trigger MMP and IL-8 expression to mediate cervical change and fetal membrane rupture. Prior to 20 weeks of gestation, the myometrium is quiescent because of the high PR-B, low ER-α, low circulating estrogen levels, and inhibition of CAP gene expression. Therefore, inflammation, abruption, and excess stretch occurring prior to 24 weeks present as "incompetent cervix" with or without subsequent PPROM and not PTL. Figure 23.6 presents schematically the discrete pathogenic processes leading to prematurity and their final common biochemical pathway.

23.4 Clinical Presentation

One-third of all patients with PTL present with intact membranes and one-third with PPROM, and one-third are the result of indicated delivery (delivery in response to maternal or fetal complications) [100].

Diagnosis of ROM is best made by sterile vaginal examination by speculum in women presenting with a suspicious clinical history or found to

have oligohydramnios on ultrasonography. Confirmation of vaginal lacerations or bony fragments may indicate pelvic fractures. Evident fluid passing through the cervical os is diagnostic.

23.5 Diagnosis

23.5.1 Prediction of Preterm Labor

23.5.1.1 Uterine Contractions

When intrauterine infection is present, an association between uterine contraction frequency and PTL has been shown [101–103]. However, uterine contractions do not predict PTL well in singletons because of the wide variation in frequency in normal pregnancy and the large overlap in frequency between women who do and do not deliver preterm [103]. Similar results were found in twins [104]; however, women admitted with a diagnosis of PTL, if they do not deliver, remain at increased risk of subsequent PTL and PPROM.

23.5.1.2 Laboratory Findings

A marked correlation of elevated CRP and ALP in women with non-acute abdomen PTL was observed when compared to women without PTL, whereas the best cutoff values of CRP >20–27 mg/L and ALP >300–399 IU/L were the best values in the prediction of PTL [105, 106]. Currently, there are no studies of prediction of PTL in pregnant patients with acute abdomen. Almost all patients with acute abdomen have elevated CRP values and therefore are at increased risk for PTL.

23.5.1.3 Transvaginal Ultrasound

Transvaginal sonography has shown that a short cervix (cervical length ≤25 mm) is associated with intra-amniotic inflammation and there is an increased risk of adverse pregnancy outcome [69, 107]. Women with a cervical length of ≤15 mm between 22 and 30 weeks of gestation have a higher rate of microbial invasion of the amniotic cavity and were more likely to deliver spontaneously before 35 weeks of gestation [108]. Therefore, the sonographic cervical length may be a useful predictor of risk of microbial invasion of the amniotic cavity and intra-amniotic inflammation [69]. Unfortunately, there are no studies in patients with localized/diffuse peritonitis or abdominal trauma when PTL develops quickly, in hours or days.

23.5.2 Preterm Premature Rupture of Membranes

An alkaline vaginal pH (6.0–6.5) with Nitrazine paper and the presence of a "ferning" pattern on microscopic examination of dried vaginal secretions are supportive (normal vaginal secretions have a pH of 5.0, whereas amniotic fluid has a pH of 7.0) when visual inspection is equivocal. These tests are subject to false-positive findings because of the presence of cervical mucus, blood, semen, alkaline antiseptics, or bacterial vaginosis and can be falsely negative with prolonged leakage and oligohydramnios. Repeat speculum examination after prolonged bed rest may provide diagnostic information if initial testing is negative despite a suspicious history. In the absence of fetal growth restriction or urogenital abnormalities, ultrasound evidence of oligohydramnios is suggestive but not diagnostic of ROM. The diagnosis can be confirmed unequivocally by indigo carmine amnioinfusion with observation for passage of dye per vaginam. A thorough search for concomitant maternal and fetal injuries is mandatory and prolonged continuous fetal monitoring strongly advocated.

23.5.3 Placental Pathology

Placental pathology has better predictive value for intra-amniotic infection than clinical signs and symptoms. Placental histology has a high negative predictive value (97%) and reasonable positive predictive value (79%) for diagnosing intra-amniotic infection compared with fluid cultures [109]. Placental pathology has a twofold improvement in positive predictive value compared with the clinical signs and symptoms of intra-amniotic infection [110]. Unfortunately, placental pathology can be obtained when the patients' management has completed without any influence in the immediate therapeutic process.

23.6 Treatment

The vast majority (70–80%) of the women with symptoms of all-cause spontaneous PTL do not deliver preterm even without intervention. The most commonly used criteria for PTL are uterine contractions (≥4/20 min or ≥8/h) *and* documented cervical change with intact membranes at 20–36w 6d.

> Women without cervical change do not have PTL and should not receive tocolysis. Women with PTL but negative fFN and TVU CL ≥30 mm have a less than 1% chance of delivering within 1 week and a more than 95% chance of delivering ≥35 weeks without therapy [111], and should therefore not receive tocolysis.

The complete diagnostic–therapeutic algorithm is presented in Fig. 23.7.

In the context of inflammation-induced PTL prevention, therapeutics should ideally eliminate the microorganism from the amniotic cavity, block the ensuing cytokine cascade that drives the release of PGs and matrix metalloproteinases (MMPs), prevent the onset of PTL, and minimize the risk of FIRS.

> Thirty-four weeks of gestation have been defined as the threshold at which perinatal morbidity and mortality are felt to be too low to justify the potential maternal and fetal complications and costs associated with inhibition of labor and short-term delay of delivery [113, 114]. Tocolytics are generally not indicated prior to viability (23–24 weeks of gestation) since these drugs do not delay delivery for more than a few days [115].

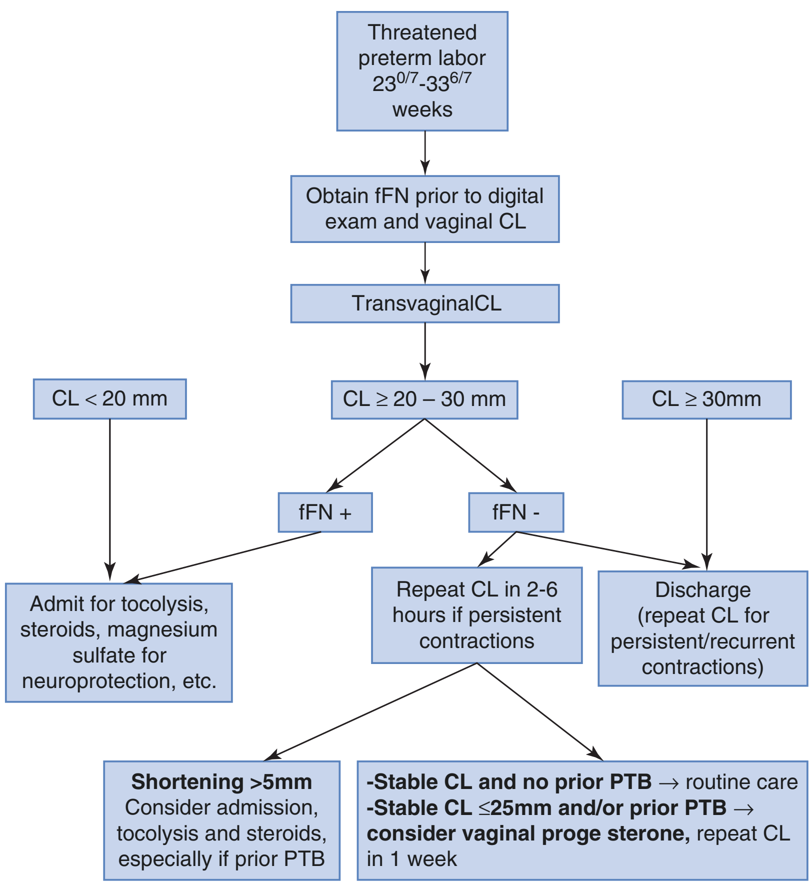

Fig. 23.7 Suggested algorithm for the evaluation and management of threatened preterm labor. – negative, + positive, *CL* cervical length, *fFN* fetal fibronectin, *PTB* preterm birth. Reproduced with permission from [112]

One of the explanations for inefficient longer delay of preterm delivery is that most interventions are directed on one of the pathways of the process of parturition. Parturition is a complex process with many perplexing pathways (see Sect. 23.2).

23.6.1 Nontocolytic Treatment

23.6.1.1 Bed Rest

Bed rest has never been tested in singleton gestations complicated by PTL or PPROM. In twin pregnancies with cervical dilatation, bed rest in the hospital has not been shown to decrease PTL [116].

23.6.1.2 Antibiotics

Intrauterine Infection

Antibiotics are routinely given to women presenting with intrauterine infection-induced PTL. However, it is not the infection but the subsequent inflammation that initiates PTL and is primarily responsible for adverse neonatal outcomes. Unfortunately, the antibiotics did not show a positive prevention of all-cause preterm birth, and even in some cases, an increase in preterm birth in some groups of women treated with antibiotics was found [117]. An exception is an improvement demonstrated in women with PPROM with antibiotics such as erythromycin. These results include an increase in latency before labor and improved neonatal outcome [118, 119].

Compared with metronidazole, clindamycin has similar activity against anaerobes but is far superior with respect to broad-spectrum activity, group B streptococcus (which is associated with PTL when present as a heavy colonization), and many other bacterial vaginosis-related organisms, particularly those more fastidious organisms such as *M. hominis* [120, 121]. Also, clindamycin have anti-inflammatory properties [122, 123]. There is merit in both oral and intravaginal administration of clindamycin for the eradication of abnormal genital tract flora/bacterial vaginosis in pregnancy. Vaginal administration delivers the highest concentration of antibiotic to the site of the heaviest bacterial load. On the other hand, bacterial vaginosis could be associated with subclinical endometritis [124], so if vaginal organisms have already gained access to the choriodecidua, these organisms may not be accessible to vaginal administration, and systemic therapy may provide benefit. There are no studies with the combined use of oral and vaginal clindamycin. Abnormal genital tract flora in early pregnancy, even if this reverts to normal, is still associated with LM and preterm birth suggesting that whatever damage is done by infection/inflammation occurs early and persists [125]. If antibiotics are used late in pregnancy when inflammatory tissue damage may have already occurred and there are already irreversible changes in the cervix, myometrium, decidua, placenta, and extraplacental membranes, then antibiotics are unlikely to be of benefit [126, 127]. Unfortunately, some of these studies were not adequately conducted.

The immune system is primed in utero and modified after birth. Accordingly, the use of antibiotics during pregnancy or the neonatal period may cause disruption of the developing neonatal gut microbiome, resulting in a failure of maturation of the immune response and the subsequent development of asthma, allergy, and atopic disease [128–131]. This has led to new initiatives for the development of new diet and gut microflora treatments for newborns.

Acute Abdomen

Studies on antibiotic prevention of inflammation-induced PTL did not include pregnant patients with acute abdomen. Therefore, there are general recommendations in these settings:

- Along with the removal of infective source, dosage and duration of antibiotic therapy are used for treating extrauterine, intra-abdominal infection as indicated by guidelines for treatment of the primary infective cause, not for the prophylaxis of uterine contractions and PTL.

- Antibiotics are recommended if group B streptococcus culture status is unknown in the pregnant patient with abdominal trauma.

Abdominal trauma patients are specific subgroup because inflammation-induced PTL is not a primary mechanism. Antibiotic treatment of all women with threatened PTL to prevent neonatal infection with group B streptococcus is recommended because preterm infants have an increased risk of this infection [132]. Rates of neonatal group B streptococcus infection and corresponding mortality rates have declined since this strategy was adopted in the USA [132]. Preterm infants with traumatic injuries and possible hemodynamic instability (due to maternal hemorrhagic shock) or blood loss are particularly susceptible to neonatal infections.

Intravenous clindamycin, in addition to other antibiotics indicated for patients with acute abdomen or abdominal trauma with unknown group B streptococcus culture status (especially before 32 weeks of pregnancy), should be administered.

23.6.1.3 Antioxidants

In vitro studies indicate that the combination of vitamins C and E can prevent tissue damage to chorioamniotic membranes inflicted by hypochlorous acid, a reactive oxygen species produced by host cells during infection and inflammation [133]. Although the dose–response relationship between the plasma ascorbic acid concentration and prevalence of PPROM has been shown, ascorbic acid concentrations may have only reflected the general nutritional status of patients [134]. The problem is that studies focused on single, for example, hypochlorous acid-induced damage [133], whereas in vivo infection-induced damage could occur via nonoxidative pathways (e.g., elastase, protease). The diet alone could be an inadequate source of vitamins C and E during pregnancy, and supplementation may be able to reduce PPROM [135]. Supplemental intake of vitamins C and E to prevent preeclampsia showed that the rates of births before weeks 37, 34, and 28 of gestation were not different. Treatment did not affect the incidence of PPROM, but respiratory morbidity was reduced [136]. The role of antioxidants in a prevention of PTL in acute settings, such as acute abdomen (peritonitis/intra-abdominal trauma), is unknown.

23.6.2 Tocolytics

Seventy years ago, it was stated that, when peritonitis is present, CS should be performed [137–139] and that Cesarean hysterectomy in the more severe cases of abscess formation may prove lifesaving. Although preterm contractions caused by uterine irritation from peritonitis occur in up to 83% of the cases, PTL and delivery occur in only 5–14%. However, more than 50% of these patients in the third trimester deliver preterm [140]. *True* PTL can be defined as uterine contractions with transvaginal CL < 20 mm or CL 20–29 mm with a positive fetal fFN [141]. *Threatened* PTL is instead the condition when a woman has symptoms of PTL, such as contractions or cramping, but no cervical change, for example, a transvaginal CL ≥ 30 mm.

Women with true PTL should receive tocolysis and corticosteroids. There is no need for therapy in threatened PTL, including tocolysis, despite symptoms [141].

For patients with true PTL, tocolytic therapy has been used to try to abolish contractions temporarily, but it does not remove the underlying stimulus that initiated the process of parturition or reverses parturition changes in the uterus and cervix. Prematurity is associated with adverse neonatal outcomes, while tocolytic agents with its intent to delay delivery have the downside that also can affect the fetus causing adverse neonatal effects. Between 23 and 26 completed weeks of gestation, each day of prolongation of pregnancy increases the survival rate by 3% [142].

Prostaglandin inhibitors and calcium channel blockers are the tocolytics with the best probability of 48 h delay in all-cause PTL, respiratory distress syndrome, neonatal mortality, and maternal side effects [143].

Compared with placebo, the probability of delivery being delayed by 48 h was highest with prostaglandin inhibitors (odds ratio 5.39) followed by magnesium sulfate (2.76), calcium channel blockers (2.71), beta mimetics (2.41), and the oxytocin receptor blocker atosiban (2.02) [143].

Tocolytic treatment after the onset of contractions could not prevent PTL and should be ordered for the patients with delayed presentation and advanced gestational age in order to prevent PTL and fetal loss [144]. Tocolysis only delays preterm delivery for a matter of days, but that ultimate preterm delivery is not prevented [145].

No study has documented positive effects on the outcome. Maybe future studies will define high-risk groups that could benefit from prophylactic tocolysis. The current recommendation is that the use of these agents is a matter of choice [146–148].

SAGES and EAES guidelines recommend tocolytics only if uterine contractions are present.

Therefore, tocolytics should not be used for prevention of uterine contractions. Tocolytics were thought to calm the uterus from the insult of acute abdomen and the intraoperative uterine manipulation, but their benefit is equivocal [149, 150]. There is no significant difference in efficacy of different tocolytics and no significant difference in outcome when tocolytics are used or not (Fig. 23.8) [151]. These findings are

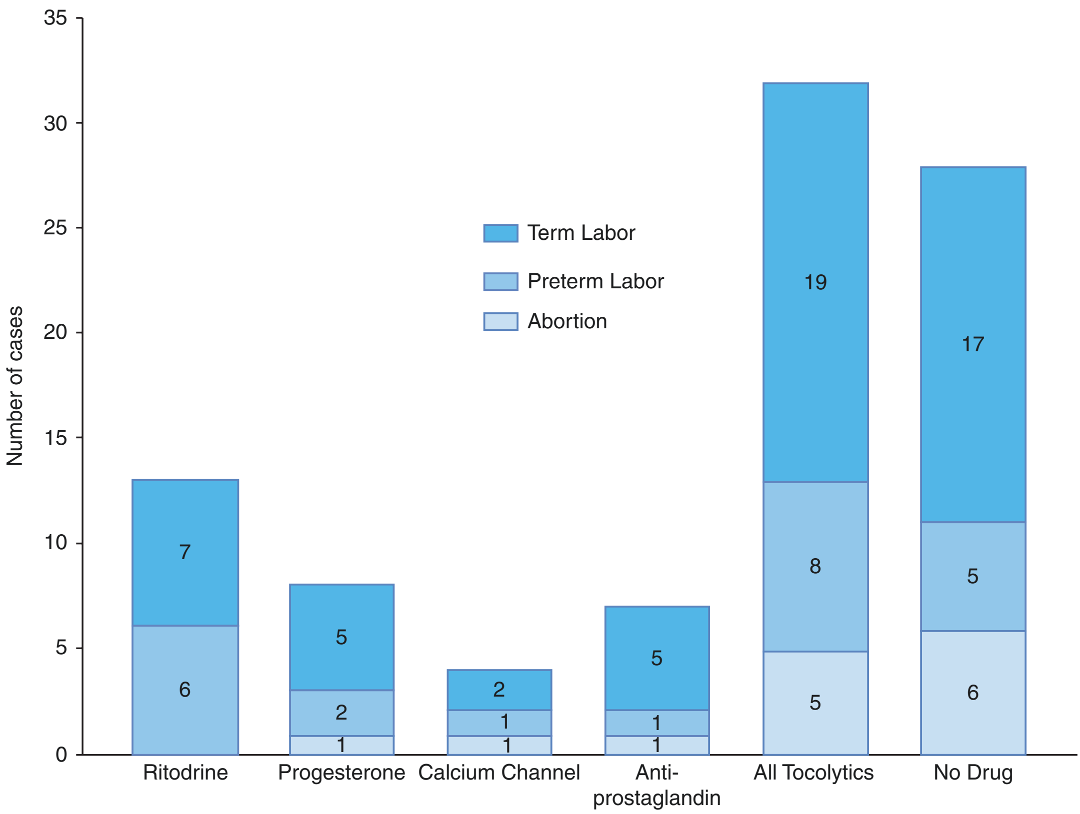

Fig. 23.8 No statistically significant difference between different tocolytics with their effect on duration of pregnancy and prevention of preterm labor in acute abdomen. Reproduced with permission from [153]

different from those which Allen et al. reported, as they recorded a 100% success rate of tocolysis in the prevention of labor [152]. On the contrary, tocolytics had serious maternal and fetal side effects, which could contraindicate their use, especially ritodrine and prostaglandin synthetase inhibitors.

Ritodrine causes maternal and fetal tachycardia, nausea, and vomiting [153, 154], so it impairs very important signs for managing acute abdomen. Unlike ritodrine and prostaglandin synthetase inhibitor, nifedipine is safer and does not alter the disease symptomatology [149]. Although nifedipine was blamed for causing hypotension, this proved to be insignificant [154, 155]. Albeit feared for teratogenicity [156], the evidence is not conclusive [157], and no malformations were reported [153].

Nearly 26% of patients with symptomatic cholelithiasis developed preterm contractions requiring tocolysis [158]. Selective use in acute cholecystitis is recommended, only if uterine contractions are present [159].

23.6.2.1 Abdominal Trauma

Trauma can cause PPROM and preterm birth and it is seldom an isolated injury. At less than 24 weeks of gestation, ROM may predispose the fetus to pulmonary hypoplasia or orthopedic deformities if the volume of amniotic fluid does not return to normal. With the injury to the placenta, hemorrhage may result in fetal anemia, hypovolemia, or both. In the absence of maternal or fetal compromise, management is usually not different from spontaneous ROM.

The use of tocolysis for the treatment of PTL due to trauma is controversial. Limited information exists regarding the use of tocolysis after blunt abdominal trauma. Because regular uterine activity after a traumatic event could result from a uterine contusion or placental abruption and these two diagnoses are indistinguishable, tocolysis is not recommended [88]. There are cases of placental abruption among women with contractions at a frequency of <1 uterine contraction every 10 min. In that population, almost 20% of women with frequent contractions had placental abruption [88]. In noncatastrophic abdominal trauma in pregnancy, tocolysis in cases of persistent contractions after the maternal and fetal testing results is found to be reassuring [160]. Slow-released progesterone should be considered in all women with contractions after abdominal trauma in pregnancy [161].

The PTL group received more magnesium sulfate tocolysis than did the term birth group (31% vs. 7%, respectively). However, there were no differences in the gestational age at abdominal trauma and the interval between trauma and delivery between groups. Cervical length, measured by transvaginal ultrasonography, is useful in predicting preterm birth [162]. In abdominal trauma, patients who later delivered preterm had a closed and no effaced cervix at the time of abdominal trauma [160]. Magnesium sulfate in non-acute abdomen PTL helps to protect the baby's brain, reduce rates of cerebral palsy, and improve long-term neonatal health outcomes despite maternal side effects (decreases respiratory efforts and, in high doses, may lead to hypotension, respiratory collapse, or cardiac arrhythmias).

> Magnesium sulfate is the tocolytic agent of choice for pregnant patients with abdominal trauma.

There are several classes of tocolytic agents not recommended in abdominal trauma. Betamimetics (β2 adrenergic agonists) cause maternal and fetal tachycardia, and they can mask the clinical signs of hypovolemia in both the mother and the fetus, leading to a delay in institution of the appropriate intervention. NSAIDs/indomethacin affects platelet function and is contraindicated in patients with head injury or occult bleeding. Calcium channel blockers may produce hypotension. Such vital sign changes mimic those seen in occult hemorrhage, mandating scrutinous monitoring.

23.6.2.2 Progesterone

Adnexal Torsion/Ovariectomy

The tocolysis includes oral or intramuscular administration of progesterone in the first trimester and oral or intravenous administration of ritodrine in the second and third trimesters [163]. If the ovariectomy is performed during the first

trimester, the patient should receive 17α-hydroxy progesterone caproate 250 mg intramuscularly weekly during 4 weeks as progestogen support for the pregnancy [164]. Possibly it protects the uterus from contractions and PTL. After this period, progesterone is produced by the placenta, and there is no need for substitution.

The administration of prophylactic tocolytics is not necessary for isolated Fallopian tube torsion during pregnancy. It can be given if there is evidence of uterine contractions [165]. There are no data about the specific influence of isolated Fallopian tube torsion on uterine irritability during pregnancy.

Abdominal Trauma

See Sect. 23.6.2.1.

23.6.2.3 Anti-Inflammatory Agents

NSAIDs/Indomethacin

Because bacterially induced PTL is associated with an increase in prostaglandin production, inhibiting the synthesis of prostaglandins is a logical therapy in cases of potential infection-induced PTL. Administration of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, has been shown to curtail the progression of both term labor and PTL [166, 167]. Currently used NSAIDs, such as indomethacin, block COX-1 and COX-2. Treatment with these drugs is associated with fetal and maternal side effects that have precluded their use [166, 168]. Prostaglandin synthetase inhibitors were blamed for reversible closure/constriction of ductus arteriosus, but when used between 26 and 34 weeks of pregnancy, the danger is minimal [169, 170]. Although antenatal indomethacin may provide enough time for antenatal steroids to improve fetal maturation, these benefits are associated with periventricular leukomalacia in premature infants [170]. The results also suggest that exposure of indomethacin within 72 h prior to delivery is associated with necrotizing enterocolitis in premature infants. Antenatal indomethacin does not appear to be associated with patent ductus arteriosus, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, and mortality in premature infants. In addition, no teratogenesis [153], altered hematological indices, or transient renal insufficiency [171] was detected.

Observations indicate that COX-2-derived prostaglandins are important for bacterially induced PTL and that COX-2 is a potentially important target for stopping PTL [172]. There are still unresolved issues about the duration and the dosage of selective cyclooxygenase inhibitors on PTL.

One of the drawbacks of prostaglandin synthetase inhibitor is its anti-inflammatory and antipyretic effect, which might mask clinical parameters for acute abdomen and give the surgeon a false sense of security. Therefore, it should be used once the diagnosis is established.

Experimental Anti-Inflammatory Agents

The following sections consider a number of promising anti-inflammatory agents with potential for use in preventing inflammation-induced PTL.

NF-kB Inhibitors

N-acetylcysteine is a nonspecific free radical scavenger and NF-kB inhibitor but is currently not in clinical use.

Sulfasalazine, a salicylate drug that blocks NF-kB activation by directly inhibiting the IKK kinases, is well tolerated and approved for use in pregnancy, with no discernible increase in the risk of fetal congenital defects, morbidity, or mortality [173]. However, increased levels of chorionic apoptosis have been reported in a human membrane model (20 h), suggesting that prolonged treatment may result in eventual membrane degradation and loss of function and structural integrity [174]. Potential use in extrauterine, intraperitoneal (acute abdomen) induced PTL is its short course use in addition to antibiotics and infection source control.

TLR4 Antagonists

Inhibition using a monoclonal anti-TLR4 antibody was effective in vivo in reducing proinflammatory mediator (TNF-α, IL-8, and

PGE$_2$) production in amniotic fluid [175] and the incidence of LPS-induced PTL [176]. Alternate TLR4 antagonists include eritoran tetrasodium [177] and TAK-242 [178], neither of which have been examined in this context. TLR4 antagonism is only appropriate in cases of gram-negative bacteria-induced PTL.

Anti-TNF-α Antibodies

The complexity of cytokine interactions associated with PTL suggests that targeting individual cytokines may not be the most optimal therapeutic intervention (Fig. 23.9). Interestingly, clinical studies have reported that maternal administration of these agents (infliximab) persists in the neonatal circulation for many weeks after birth [179] and may, therefore, dampen both intrauterine and fetal inflammations protecting the fetus from the adverse sequelae of intrauterine infection and inflammation. In addition, these agents could be used for treating some of the causes of the acute abdomen during pregnancy (Crohn's disease). There is little evidence for congenital abnormalities with the use of anti-TNF-a therapy during pregnancy [180], but high levels in fetal circulation may increase the risk of neonatal infection. All these facts should be weighed against the consequences of PTL caused by acute abdomen.

Cytokine-Suppressive Anti-inflammatory Drugs (CSAIDs)

CSAIDs specifically target the NF-kB and p38 MAPK signaling pathways with demonstrated efficacy in animal models [181–183]. These agents have a potential to be more effective and selective than NSAIDs for the inhibition of inflammation-induced PTL, as they directly tar-

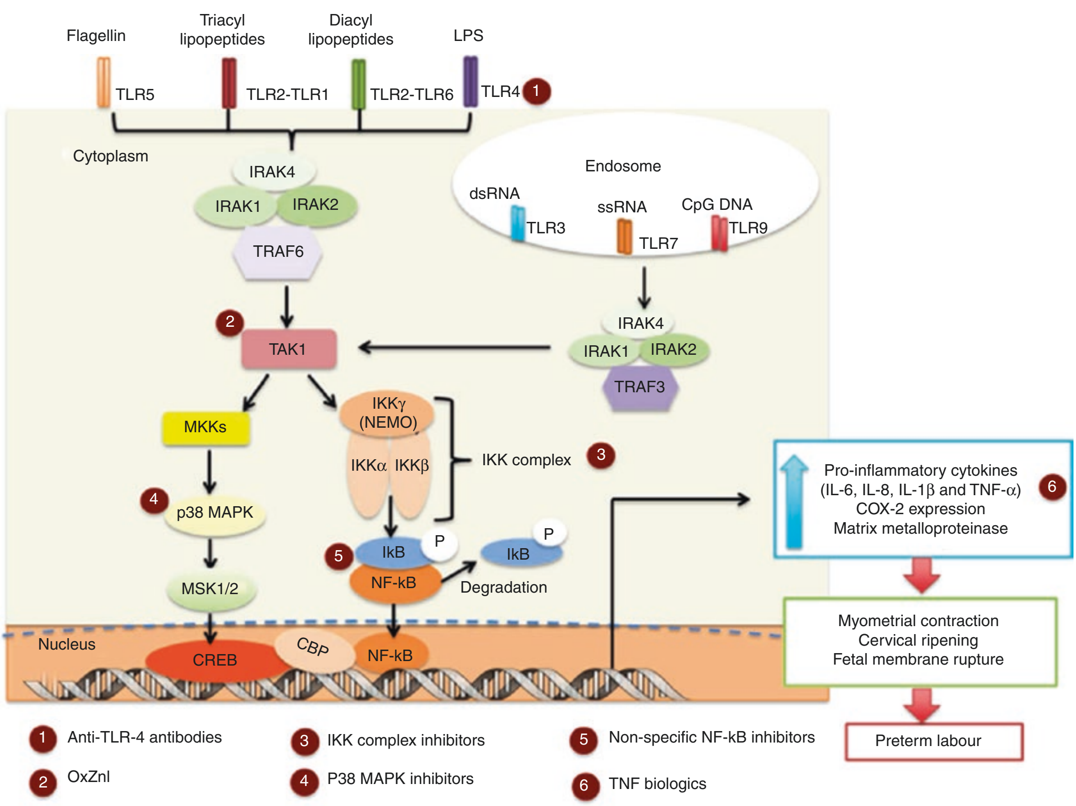

Fig. 23.9 Infection-induced preterm labor triggered by activation of TLR-mediated NF-kB and p38 MAPK inflammatory signaling cascades. Targets for the selected anti-inflammatory agents are indicated in red circles (Reproduced from [184] under the CC BY 4.0)

get signaling molecules without interfering with the constitutive/homeostatic roles of prostanoids (Fig. 23.8). Importantly, depending on the route of administration and placental transfer properties, CSAIDs may have the potential to block intra-amniotic and fetal inflammation, thereby protecting the fetus from the adverse sequelae of exposure to inflammatory mediators.

23.6.2.4 Betamimetics

Betamimetics are not indicated in patients with acute abdomen. Ritodrine should not be used in cases of bowel obstruction or toxic megacolon due to its influence on colonic dilation [185, 186].

23.6.3 Combination Treatment

23.6.3.1 Combination Tocolysis

It is unclear whether a combination of tocolytic drugs for PTL is superior to single-agent tocolysis due to a lack of large, well-designed trials. There are no trials in patients with acute abdomen.

23.6.3.2 Tocolysis and Nontocolytic Agents

There is only one study in non-acute abdomen patients in which using very strict entry criteria, a therapeutic cocktail of interventions, including antibiotics, steroids, and tocolytics, demonstrated neonatal benefit primarily by prolonging gestation [187].

> A single antenatal course consists either of 2 × 12 mg betamethasone IM, 24 h apart, or 4 × 6 mg dexamethasone IM every 12 h, after 24 weeks of gestation.

The duration of fetal benefit after a course of glucocorticoids is uncertain. A repeat course might confer a modest additional neonatal benefit, whereas multiple courses can reduce fetal growth [188]. Beneficial effects include the reduced occurrence of respiratory distress syndrome, intraventricular hemorrhage, neonatal death, necrotizing enterocolitis, patent ductus arteriosus, and bronchopulmonary dysplasia [189].

In patients with acute abdomen, antibiotics are used as indicated for the underlying disease, either as prophylaxis or therapy.

23.7 Prognosis

All-cause preterm births account for 75% of perinatal mortality and more than half the long-term morbidity [190]. Although most preterm babies survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications.

Fetal bacteremia was found in 33% of fetuses with positive amniotic fluid cultures and in 4% of those with negative amniotic fluid cultures in the context of PPROM. Therefore, subclinical fetal infection is far more common than traditionally recognized. Recently, it was shown that 23% of neonates born between 23 and 32 weeks of gestation had positive umbilical blood cultures for genital mycoplasmas [191].

23.7.1 Fetal Inflammatory Response Syndrome

The majority of fetuses exposed to chorioamnionitis develop a systemic inflammatory response known as the fetal inflammatory response syndrome (FIRS) [192, 193]. This is due to the fetus being in direct contact with the infected amniotic fluid and/or inflammatory cell transfer from the uteroplacental circulation. FIRS can itself be categorized as clinical or subclinical. Clinical FIRS is defined by a fetal plasma IL-6 >11 pg/mL [194], while subclinical FIRS is defined histologically by funisitis and fetal vasculitis [193]. Fetuses with an elevated plasma IL-6 concentration had a higher rate of severe neonatal morbidity and a shorter cordocentesis-to-delivery interval than those with an IL-6 concentration lower than 11 pg/mL. The disorder can also be diagnosed by the measurement of C-reactive protein concentrations in umbilical cord blood. Fetuses with FIRS have more systemic involvement, including

hematologic abnormalities (neutrophilia), and a higher median nucleated red blood cell count than those without elevated IL-6. In addition, they have evidence of fetal stress, as determined by the fetal plasma ratio of cortisol to dehydroepiandrosterone sulfate (DHEAS), congenital fetal dermatitis, fetal cardiac dysfunction, involution of the thymus, and abnormalities of the fetal lung and brain. Among patients with PPROM, elevated fetal plasma IL-6 is associated with the impending onset of PTL, regardless of the inflammatory state of the amniotic fluid. This suggests that the human fetus plays a role in initiating the onset of labor.

However, maternal–fetal cooperation must occur for parturition to be completed. Fetal inflammation has been linked to the onset of labor in association with ascending intrauterine infection. However, systemic fetal inflammation may occur in the absence of labor if the inflammatory process does not involve the chorioamniotic membranes and decidua. Such instances may take place in the context of hematogenous viral infections or other disease processes (e.g., rhesus alloimmunization).

Affected fetuses have evidence of multi-organ involvement with a higher rate of severe neonatal morbidity after adjustment for gestational age, and cases of PPROM had a shorter cordocentesis-to-delivery interval. Neutrophilia is present in two-thirds of fetuses with FIRS, whereas neutropenia is observed in 7%. FIRS is associated with BPD. Amniotic fluid and its contents can be inhaled by the fetus and reach the distal parts of the airways and the alveoli. FIRS is found in 76% of infants with atypical chronic lung disease (defined as chronic lung disease in the absence of respiratory distress syndrome). Bacterial products and cytokines may contribute to the myocardial depression. Fetuses that are unable to modify their cardiac compliance or maintain ventricular cardiac output may suffer an inadequate brain perfusion, predisposing to hypotension and brain ischemia in utero. This could create conditions for the development of periventricular leukomalacia and brain injury.

23.7.2 Fetal Mortality

As early as 1912, it was observed that the infection may extend to the uterus from the Fallopian tubes, the broad ligaments, and the uterine wall to the placenta [195]. In diffuse peritonitis, fetal death in utero is caused probably by transplacental diffusion of bacteria [196]. Fetal microbial invasion results in FIRS that can progress toward multiple organ dysfunction, septic shock, and death in the absence of timely delivery. Due to the small number of patients, it is difficult to compare the influence of therapeutic delay, type of the microorganism involved, and proven route of infection. In the acute abdomen, it is questionable whether the acute chorioamnionitis has enough time to develop. Also, cases of subclinical chorioamnionitis are missed resulting in underestimation of this condition.

The risk of fetal death due to pyrexia, as distinct from infection, may have been overstated [197], and some drugs used in treating severe infections may be teratogenic, thus compounding the effect of pyrexia. Possible effects of maternal pyrexia on the fetus and neonatal development are described in Sect. 23.7.3.

23.7.3 Fetal Morbidity

23.7.3.1 Neurologic

Epidemiological evidence is linking perinatal brain injury, in particular, cerebral palsy, periventricular leukomalacia, and intraventricular hemorrhage, with intrauterine inflammation [198–202]. Exposure to histological chorioamnionitis combined with impaired placental perfusion has been demonstrated to increase the risk of poor neurological and neurocognitive outcomes at 2 years of corrected age in children born very preterm [203]. Similar observations were made at 8 years of age in children exposed to severe histological chorioamnionitis [204]. Histological chorioamnionitis is also associated with an increased incidence of speech delay and hearing loss at 18 months of corrected age in infants born

very preterm [205]. Furthermore, histological chorioamnionitis caused by bacterial and viral infection has been associated with an increased risk of autism spectrum disorders [206, 207] and schizophrenia [207–209].

There are several potential mechanisms for associations between chorioamnionitis and adverse neurological outcomes. Intrauterine inflammation is linked with diffuse white matter injury in the brain of preterm neonates, due to activation of a systemic inflammatory cascade [200, 201, 203, 210]. Chorioamnionitis has been associated with impaired fetal and newborn cardiac function [211, 212], which may compromise brain blood flow due to lower blood pressures [201, 211, 213]. This results in altered cerebral oxygen delivery. Impaired cerebral autoregulation is considered one of the main contributors to brain injury in the preterm neonate [202, 214]. Impaired cerebral autoregulation may be more prevalent in neonates born after exposure to intrauterine inflammation [213, 214], but the direct proofs are limited. Data from animal experiments are consistent with human studies in showing effects of intrauterine inflammation (with various routes of microbe inoculation) on the developing brain in the form of (1) karyorrhexis (nuclear fragmentation) of glial cells and reduced density and disorganization of white matter [215], (2) astrocytosis and a reduction in oligodendrocyte number in subcortical white matter [216], (3) diffuse damage and focal periventricular leukomalacia [217], and (4) decrease in myelination, potentially due to reduced numbers and/or function of oligodendrocytes [218]. Currently, it is not known whether the a) location of the primary infective focus, b) the route of infection dissemination, and/or c) the duration and severity of infection have different central nervous system (and another organ) consequences.

Cerebral Palsy

Prematurity has a strong association with cerebral palsy; one-third of all neonates who later have signs of cerebral palsy weigh less than 2500 g. Newborns with birth weights less than 1500 g have a rate of cerebral palsy 25–31 times higher than those with a normal birth weight. The most common form of cerebral palsy affecting preterm babies is spastic diplegia. In turn, preterm babies that subsequently develop spastic diplegia have a high rate of PVL. Strong evidence links the brain injury and infant exposure to perinatal infection and inflammation. In 1955, Eastman and Deleon observed that intrapartum maternal fever was associated with a sevenfold increase in the risk of cerebral palsy. In 1978, data from the Collaborative Perinatal Project showed that among low birth weight infants, chorioamnionitis increased the risk of cerebral palsy from 12/1000 to 39/1000 live births.

Epilepsy

Epilepsy is the most common serious neurologic disorder of childhood [219–221]. Before the age of 15 years, 1–1.7% of all children will have at least one unprovoked seizure, and up to 0.8% will have repeated seizures [220]. The incidence of childhood epilepsy is highest in the first year of life – about 150/100,000 person-years, falling to around 50/100,000 person-years after age 9 years [220].

The etiology of epilepsy is poorly understood [219, 220], with no known risk factor in many cases [219, 222, 223]. Generalized epilepsies often can be traced infection [220]. In particular, insults acting during the prenatal and to single-gene mutations or chromosomal abnormalities, while partial epilepsies are frequently triggered by external insults to the central nervous system, including brain injury and central nervous system neonatal period, are thought to contribute to the etiology of some epilepsies [219, 220, 224]. Observation of a seasonal pattern, i.e., an excess of births during winter months among children who develop epilepsy [225, 226], led to the suggestion that prenatal exposure to maternal infection may be a risk factor. Any maternal infection during pregnancy (method of measurement unspecified) was associated with a 1.0–1.6-fold increase in the risk of childhood epilepsy [224]. Maternal self-reported history of cystitis, pyelonephritis, vaginal yeast infection, and/or symptoms of infection (diarrhea,

coughs) during pregnancy was associated with a 1.2- to 2.6-fold increased risk of epilepsy among offspring [227]. Risk varied by type of infection and was the highest for a self-reported vaginal yeast infection (2.6-fold) and pyelonephritis (2.3-fold) [227]. Therefore, there is a 40% increased risk of epilepsy associated with prenatal exposure to maternal systemic infection [228]. This association could be caused by the infection itself, by its antecedents or consequences, or by antibiotic treatment. However, the similar magnitude of increased risk observed for different types of antibiotics argues against the role of specific types of infections or specific treatments. Maternal infections of different types, measured by self-report collected twice during pregnancy and additionally at 6 months after delivery, were associated with epilepsy in offspring [227].

Children with prenatal exposure to more than two maternal fever episodes, maternal fever with urinary symptoms or maternal fever of 39.0 °C, did have an increased risk of epilepsy – suggesting that the underlying causes of fever rather than elevated temperature, such as sauna use, play a role [229]. Recently it has been suggested that inflammation may be involved in the mechanism linking fever and epilepsy [230]. Experimental studies in rodents have shown that inflammatory reactions in the brain can enhance neuronal excitability [231] and anti-inflammatory treatments reduce seizures in experimental models.

Cytokines are key players in the modulation of neuronal excitability, as well as in leukocyte recruitment, and inflammatory central nervous system infections [230], yet little is known about their role in the pathogenesis of epilepsy. It is possible that maternal cytokine production in response to an infection during pregnancy induces fetal neurological injury [232]. Findings of a nearly threefold increased risk for epilepsy among children born to mothers with epilepsy suggest that infants genetically predisposed to epilepsy may be more susceptible to inflammatory reactions [228].

Premature births result in 75% of neonatal deaths and most neonatal intensive care unit admissions [233]. A substantial effect of premature birth on long-term physical and mental health is observed [234]. Babies born at <28 weeks gestational age spend 85 times longer in the hospital than babies born at term, representing a considerable health-care cost [235]. Even among babies born after 32 weeks, educational and behavioral problems can occur in 33% at 7 years of age [236], with 25% of children born between 32 and 35 weeks gestational age requiring support from non-teaching assistants at school [237].

Low birth weight is associated with poor outcomes in cognitive function, academic achievement, and behavior and social adaptation [238, 239]. Low birth weight is also associated with an increased risk of cardiovascular disease and other chronic illnesses [240].

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G. Augustin, *Acute Abdomen During Pregnancy*, https://doi.org/10.1007/978-3-319-72995-4

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